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CHROMIUM (III) AND COPPER (II) COMPLEXES WITH SALBUTAMOL AND SULPHADOXINE : KINETIC STUDIES IN 80% ETHANOL – WATER MEDIUM

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ABSTRACT

The stability constants for the copper (II) and chromium (III) ions with drugs such as salbutamol and sulphadoxine have been studied using pH-measurements in 80% (v/v) ethanol-water medium. The value of proton-lingand stability constants and metal-ligand stability constants are calculated. The stability of the chromium (III) complexes is greater than that of copper (II) complexes.

Key words: Binary complexes, Stability constants, pK.

INTRODUCTION

Majority of diseases are caused by microorganism[1]. It is necessary to kill and remove the microorganism from daily need articles and foodstuff. When such organism enters in a body, they multiply fastly, weakened the body defense factor and causes a disease. A substance used for cure of an ailment or alleviation of symptoms is called drug or medicine. Several types of drugs[2] such as antileprotic, high-ceiling diuretics, antibacterial etc. and their metal complexes have special importance in bio-chemical systems. Some metal ions present in biological fluids e.g. copper and chromium are energy sources of life.

The protonation study of drugs[3] in aqueous medium has already been studied by several workers. Little information is available about the stability constants of drug and metal complexes in non-aquesous and ethanol-water mixed solvents, with respect to their protonation and stability constants or solvation properties[4-6]. *In vivo* reactions are considered to take place in aqueous medium. Recently, it has been observed that solvent such as ethanol

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is a good media for *in vivo* reaction[7]. The study on proton-lingand and metal ligand stability constants of drugs complexes in ethanol-water medium will be useful for understanding of drugs intake in living organisms.

In present work, the proton ligand stability constant and stability constant of drugs with copper (II) and chromium (III) metals have been studied potentiometrically in 80% (v/v) ethanol-water mixture.

EXPERIMENTAL

Drugs samples of salbutamol and sulphadoxine in pure form were obtained from pharma industries and used as received. Ethanol was purified as described in literature.[8] Double distilled water was used for the preparation of both ethanol-water mixtures and stock solution of drugs.

All chemicals used were of AnalaR grade. $NaClO_4$ (0.1M) and NaOH solution were prepared in carbon dioxide free double distilled water. $HClO_4$ Reidal (Germany) was used for the preparation of the stock solutions of copper (II) and chromium (III) to prevent hydrolysis.

All pH -metric titrations were carried out at 27^0C in an inert atmosphere by bubbling oxygen free nitrogen gas through an assembly containing the electrodes in order to prevent atmospheric oxidation using carbonate free NaOH. The pH of the solution was measured using Elico model L1-120 Digital pH meter and Elico (pH-13) type Ek-62A glass electrode. Following three solutions were titrated separately against standard carbonate free NaOH.

(i) Free $HClO_4$

(ii) Free $HClO_4$+ Ligand (drug)

(iii) Free $HClO_4$+ Ligand (drug) + Metal ion

For the determination of the proton-ligand stability constants, stock solutions of free perchloric acid, drug and sodium perchlorate were taken in a 50 mL volumetric flask, followed by ethanol to obtain solutions of the desired concentration and percentage of ethanol. The contents were diluted upto the mark. Aliquots of 50 mL were transferred to the pH metric cell and titrated against standard NaOH solution.

For the determination of metal-ligand stability constants of drug with metal ions, suitable amounts of metal ion, drug and perchloric acid stock solutions were taken into pH

metric cell and titrated against NaOH solution until a precipitate was just observed in titration cell. At this point, titration was stopped. During each titration, ionic strength of solution was maintained by adding 0.1 M $NaClO_4$. pH meter reading were after taken every fixed interval until stable values were obtained. pH meter readings in 80% (v/v) ethanol-water were corrected by method of VanUirt and Hass[9].

Proton-ligand stability constant and metal-ligand stability constant of drugs-metal ion complexes were calculated with the help of computational programme, to minimize the standard deviation.

RESULTS AND DISCUSSION

The proton-ligand stability constants of salbutamol and sulhadoxine and the metal-liagand stability constants of their copper (II) and chromium (III) were determined in 80% (v/v) ethanol-water at 27^0C and ionic strength μ = 0.1 M ($NaClO_4$). The results are given in Table 1.

Table 1: The proton-ligand stability constants of salbutamol and sulphadoxine and the metal-ligand stability constants of their copper (II) and chromium (III) determined in 80% (v/v) ethanol-water and 27^0C and ionic strength μ = 0.1 M (NaClO4).

Drugs	pK			Metal ions	
	pK_1	pK_2		Cu^{2+}	Cr^{3+}
Salbutamol	10.1995	-	$\log k_1$	2.7783	2.8309
			$\log k_2$	-	-
			$\log \beta$	2.7783	2.8309
Sulphadoxine	7.6012	9.8989	$\log k_1$	3.524	8.1961
			$\log k_2$	-	-
			$\log \beta$	3.524	8.1961

The basicities of the ligand have been measured in terms of their proton-ligand stability constants. The determination of proton-ligand stability constant of the ligand is a prerequisite for the evalution of metal-ligand stability constant. Hence, proton-ligand stability constants of the ligands have been determined by Irving-Rossotti's pH metric titration technique.[10]

The titration curve for salbutamol and suplhadoxine show buffer region in pH > 7. The release of proton in the lower buffer region indicates the dissociation of proton from protonated nitrogen atom. From the acid and ligand titration curves, the value of $\bar{n}_A$ have been calculated using Irving-Rossotti method[11] and further by computational programme.

The $\bar{n}_A$ values range between 0.1 and 1 for salbutamol indicating the liberation of one proton and 0.1 and 2 for sulphadoxine indicating the liberation of two proton. The pK values for salbutamol and sulphadoxine were determined pH meterically.

The pK value of salbutamol was found to be greater as compared to the pK value of other drugs. Therefore, it is more basic in nature. The greater pK value of salbutamol is explained on the basis of the intrinsic nature of the basic site and inter-molecular hydrogen bonding[14,15]. The pK value of sulphadoxine was also found to be greater. This can be explained on the basis of strong + mesomeric effect[13] of oxygen atom with its loan pair of electrons. Thus, the order of pK values of the ligands is as follow, which shows a good agreement with pK value in aqueous medium[15-20].

Salbutamol > Sulphadoxine

pH decreases, if a neutral metal ion solution is added to the ligand solution. The metal-ligand titration curve lies below the pure ligand titration curve. The pH of complex formation is much below than the pH of metal ion hydrolysis. These features of the pH metric studies confirm the formation of complexes by all the metal ions with drugs.

The metal ligand formation curve data for salbutamol and sulphadoxine with copper (II) and chromium (III) indicates that the $\bar{n}$ values range between 0.2 to 0.8. This suggests that metal ions form 1 : 1 complexes[20] with drugs in solution. log k values evaluated by the computational technique are in good agreement with each other. The binary formation constant so obtained are presented in Table 1. The order of log k_1 > log k_2 is commonly observed[12]. The reason is statistical effect i.e. statistically, coordination of a second molecule is difficult, when compared to the first due to availability of less number of coordinating sites on the mtal ion for the second ligand. The standard deviation for various metal-ligand system is within 0.036.

The ligand salbutamol and sulphadoxine contain different coordinating sites. The release of proton in the pH range of these ligands in the present investigation indicate that –OH group of salbutamol is participating in bonding with metal ion. It is confirmed that

these ligands act as oxygen donors. The perusal of the stability data reveals that the overall stabilities with respect to ligand in the order in accordance with their relative basicities is -

Salbutamol > Sulphadoxine

Irving and Rossotti[21] have proposed a relation between the stability of the complexes and basicity of the ligand by equation.

$$\log k = a\ pK + b \qquad \ldots(1)$$

The relation graph shows a straight line and the value of slope should be unity for a series of closely related ligands. In the present study, such relationship does not exist, since the drugs used are of diverse in nature.

The stability constants of metal-ligands such as salbutamol and sulphadoxine show a good agreement with Irving-William order of stability constant[22, 27-28].

Cu (II) < Cr (III)

The stability constants of Cu (II) with ligands indicate that the weakly basic copper[23] forms stronger complex. It suggest that strength of bonding in these comelxes depends on the ability of the metal to form homopolar bond between the metal and ligand. The another reason for the higher stability constant of copper is that the copper has single ‘s’ electron outside the filled third shell. The filled ‘d’ electrons are involved in metallic bonding. This factor contributes too much to more noble character of copper so to make compounds more covalent.[24] Cu^{2+} has greater lattice and solvation energies and hence, higher stability constants for complexes of Cu^{+2} ion are observed.

Salbutamol and sulphadoxine interact with metal ions Cu (II) and Cr (III) to form normal (ML) and bis binary (ML_2) complexes[25,26]. These ligands form stable complexes with Cu (II) and Cr (III) due to the formation of more stable five membered chelate ring, but it is observed that Cr (III) form more stable five membered ring with these ligand than Cu (II), because of higher charge on metal ion and smaller size.

Sulphadoxine also form stable complexes with Cu (II) and Cr (III) but the complex with Cr (III) is more stable than Cu (II), because of higher charge on metal ion and smaller size[23, 29].

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REFERENCES

1. D. A. Williams and L. T. Lemke, Foye's Principles of Medicinal Chemistry 5th Edition (2205).
2. J. Maslawska and L. Chruscinki, Polyhydron, **5**, 1135 (1986).
3. F. Gharid and M. Mollaie, J. Chem. Eng. Data, **44**, 77 (1999).
4. A. Dogan, F. Koseoglu and E. Kilic, Anal Biochem, 295, 237 (2001).
5. L. D. Hughes, J. J. Bergan and J. E. Grabowski, J. Org. Chem., **51**, 2579 (1986).
6. D. D. Perrin and W. L. F. Armarega, Purification of Laboratory Chemicals, Pergamon Press, Elmsford, New York (1991).
7. L. G. Van-Vitart and C. G. Hass, J. Am. Chem. Soc. **75**, 451 (1953).
8. H. M. Irving and H. S. Rossotti, J. Chem. Soc., 2904 (1954).
9. P. Narendra, D. Sudarshan Reddy, D. Madhava Reddy and B. Satyanarayana, Res. J. Chem. Environ., **7** (2003).
10. V. D. Bhosale, S. S. Shetye and K. C. Vichare, Asian J. Chem., **16**, 1, 338 (2004).
11. Radha, Thesis Submitted to Andhra University (2005).
12. A. W. David, Medicin. Chem., 1070-1080 (2005).
13. C. Hansch, Comprehensive Medicinal Chemistry, **Vol. 6**, New York (1990).
14. A. Albert and E. P. Serjeant, Determination of Ionization Constants 3rd Ed. (1984).
15. A. E. Martell and R. J. Motekaitis, VCH Publisher Inc., (1988) pp. 159-196.
16. M. Bhattacharya, Iqbal, and S. Malik, Asian J. Chem., **18**, 715 (2006).
17. V. N. Bhosale, S. R. Mirgane and B. R. Arbad, Oriental J. Chem., **20(3)**, 597 (2004).
18. H. Irving and Williams, Nature, **162**, 741 (1948).
19. J. J. Vora, Sharma Sangita, J. G. Gurjar, R. A. Patel and R. H. Choudhary, Int. J. Chem. Sci., **1(2),** 115 (2003).

20. H. C. Zahid, T. S. Claudil and S. J. Andrea, Enz. Inhib. Med. Chem., 1475 (2005).

21. Dreensek, Petra, L. Ivan, T. Iztok, G. Gerald and T. Ekkehart, Acta Crystallograph. C, 108 (2003).

22. B. Satyanarayana, P. Somaih Verra and P. Madhava Reddy, Res. J. Chem. Environ., **10** (2006).

23. S. D. Deosarkar, M. L. Narwade, Oriental J. Chem., **24**, 295 (2008)

24. Pratibha Mital, Neeta Kanoongo and V. Uma, Oriental J. Chem., **24**, 303 (2008).

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