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SYNTHESIS AND ANTIBIOLOGICAL ACTIVITY OF ZN(II) AND MN(II) COMPLEXES OF MIXED ANTIBIOTICS

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ABSTRACT

In this investigation, mixed ligand metal complexes of ampicillin and oxytetetracycline prepared by using Zn(II) and Mn(II) metal chloride were reported and characterized based on some physical properties. Physicochemical properties helpful in biological activity. Polarographic technique was used to determine the stability constants (logβ) and thermodynamic parameters (ΔH, ΔG, ΔS) of metal complex with oxytetracycline as primary ligand and ampicillin as a secondary ligand at PH 7.30 ±0.01 and an ionic strength μ= 1.0 $NaClO_4$ at 25 °C and 35 °C. The synthesized complexes were also screened for their antibacterial activity against Escherichia coli and Staphylococcus aureus by using agar diffusion method. Antibacterial activity of the complexes in vivo for sensitivity test has been screened. The result show that most of the metal complexes were more active than the neat ligand, against these bacterial species as expected.

KEYWORDS: [Metal-oxytetracycline-ampicillin] complex, antibacterial activity, physicochemical property.

INTRODUCTION

Metal complexes play an important role in many biological systems.[1,2] It has been observed that metal ions have considerable effect on the antimicrobial activity of antibiotics.[3] Metal ions accelerate drug actions. In many cases coordinated metal ions in antibiotics play an important role in maintaining proper structure and or function of these antibiotics thereby increasing antibacterial activities of the drugs.[4]

Some physicochemical property helpful in biological activity. With this view, in this study, some metal complexes of antibiotics have been screened for their activity towards E. coli and Staphylococci aureus.

In this paper reported the stability constants and thermodynamic parameters of [Zn-oxytetracycline -ampicillin] and [Mn- oxytetracycline -ampicillin] mixed systems at 25 °C and 35 °C.

MATERIAL AND METHODS

Metal salts used were of analytical grade. Solutions of metal salts were prepared in millipore water. The metal salt solutions were standardized by appropriate standard methods. Ampicillin trihydrate and oxytetracycline hydrochloride was obtained from Rajrab pharmaceutical company IIorin Nigeria. E. coli and Staphylococcus aureus were obtained from the department of microbiology, Dr. H. S. Gour University, Sagar.

Synthesis of complex

4.035 gm (0.01 mole) of ampicillin tryhydrate was mixed with 4.604 gm (0.01 mole) of oxytetracycline hydrochloride in a beaker. The mixed ligands was carefully poured into round bottom flask .The beaker was rinsed into the round bottom flask with 10 ml of distilled water. Then solution of $ZnCl_2$ (0.01 mole) in 10 ml of distilled water was added. The solution was refluxed for 3 hours which it was cooled in a refrigerator. The resulted precipitate was filtered, recrystallized from ethyl alcohol and dried in a desicator for one week. The same procedure was repeated for $MnCl_2$ salt. The complexes were stored in airtight bottles.

Stability Constant and Thermodynamic parameters

The stability constant of ternary complexes were evaluated by polarographic technique by employing Schaap and Mc master method.[5] Which confirmed the stoichiometry of the complexes.

The thermodynamic functions (ΔG, ΔH and ΔS) has been calculated by following equations[6,7]

$$\Delta H = \frac{2.303\ RT_1T_2\ (\log K_2 - \log K_1)}{T_2 - T_1} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ (1)$$

$$\Delta G = -2.303\ RT \log K \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ (2)$$

$$\Delta S = \frac{\Delta H - \Delta G}{T} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ (3)$$

Stability constant and thermodynamic parameters are recorded in Table 1 and Table 2 respectively.

Antibacterial activity

The antibacterial activity of antibiotics (AMP and OXY) and its metal (Zn and Mn) complexes was checked by disc diffusion technique and reported in Table-3.This was done on E.coli and Staphylococci aureus at 25°C.The disc formed by whatman filter paper NO.1 and diameter 6 mm was soaked in the aqueous solution of compound. Minimum inhibitory concentration (MIC) of oxytetracycline and ampicillin 34 µg/ml taken. Ternary complex of antibiotics are in the range of 50 µg/ml to 100 µg/ml are taken.

Table 1: Stability constant of antibiotic complexes.

Metal	Temperature	logβ(Stability constant)		
		logβ11	logβ12	logβ21
Mn(II)	25°C	-	6.53	8.56
	35°C	-	6.24	8.12
Zn(II)	25°C	5.123	8.123	10.52
	35°C	4.800	7.753	9.990

Table 2: Thermodynamic parameter of antibiotic complexes.

Metal	-ΔH K cal/ mol			-ΔG K cal/ mol			-ΔS cal/deg/ mol		
	logβ11	logβ12	logβ21	logβ11	logβ12	logβ21	logβ11	logβ12	logβ21
	(35°C -25°C) For difference of 10°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
Mn(II)	-	11.341	18.482	-	8.905	11.674	-	8.174	22.845
				-	8.823	11.445	-	8.175	22.847
Zn(II)	13.567	15.541	-	6.986	11.078	14.348	21.673	14.976	26.697
				6.765	10.928	14.081	21.684	14.977	26.698

ΔH= CHANGE IN ENTHALPY

ΔG= CHANGE IN FREE ENERGY

ΔS= CHANGE IN ENTROPY

Table 3: Antibacterial activities of Ligand and Metal complexes.

INHIBITION AREA UNIT(mm)

	Escherichia coli	Staphylococcus aureus
AMP	40	42
OXY	32	34
Mn(II)- OXY-AMP	44	43
Zn(II)-OXY-AMP	46	45

AMP= AMPICILLIN

OXY= OXYTETRACYCLINE

RESULT AND DISCUSSION

The stability constants of ternary complexes have been evaluated by polarographic technique by employing Schaap and Mc master method which confirmed the formation of 1:1:1, 1:1:2 and 1:2:1 complexes. The value of stability constant which reported in Table 1, showed the Zinc complex are more stable than Mn complex and also found that complex are more stable at 25°C as compared to at 35 °C.

Thermodynamic parameters are very important to understand the temperature effect on the stability of complexes or to interpret the binding of metal ligand complex.

The thermodynamic parameters of the [Metal-oxytetracycline-ampicillin] complexes were given in Table 2. It is clear from the thermodynamic parameters[8] of complexes that, the stability constant (logβ) decreased with increased of temperature, confirming that complexes are not stable at higher temperature and increasing stability suggesting lower temperature favors the chelation process. It can be seen that negative value of ΔG indicates the spontaneity of the complex. Table 2 shows that the values of ΔG is less negative at higher temperature and ΔS is more negative at higher temperature confirmed that the complex are not stable at higher temperature. The ΔH is negative in all complexes. The negative ΔH suggests that [Metal-oxytetracycline-ampicillin] is exothermic. It means greater the amount of heat released in reaction, more stable are the reaction products. The change in entropy (ΔS) is negative in all complexes. The negative value of ΔS corresponds to a more ordered complex and this implies a small value of the steric factor.

The AMP show inhibition with Escherichia coli and Staphylococcus aureus with 40 and 42 mm inhibitory zone respectively and the OXY show inhibition with Escherichia coli and Staphylococcus aureus with 32 and 34 mm inhibitory zone (Table-3) respectively . The ternary complex of antibiotics with Zn (II)and Mn(II) metal ions show higher antibacterial activity as compared to parent drug(AMP and OXY).

The result of antibacterial screening indicate that the metal complex show more activity than parent drug. This may be due to higher stability of the metal complex than parent drug.

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