# Kinetics and Mechanism of Oxidation of [4s, 4as, 5as, 12as]-4-(Dimethylamino)-1,4,4a,5,5ab,11 12a octahydro 3,6,10,12,12a-pentahydroxy-6-methyl-1,11 dioxo napthacene carboxamide hydrochloride (Tetracycline hydrochloride) with Bi(V) in HClO$_4$-HCl mixture

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**ABSTRACT:** Bismuth (V) has been stabilised in strong acidic solution by acidic mixture and the complex formed was elucidated spectrophotometrically. Stoichiometry of Bi (V) oxidation of tetracycline (TC) in acidic medium was established in the pH range 2.0-3.0 by iodometric and spectrophotometric methods. The oxidation follows first order kinetics in Bi (V). Oxidation products have been proposed. Dependence of reaction rate on temperature has been studied and Eyring's parameters were computed. A plausible mechanism consistent with the observed results has been proposed.

Keywords: Bismuth(V), tetracycline, oxidation, mechanism, kinetics.

## INTRODUCTION

Tetracycline having chemical name [4s, 4as, 5as, 12as]-4-(Dimethylamino)-1,4,4a,5,5ab,11 12a octahydro 3,6,10,12,12a-pentahydroxy-6-methyl-1,11 dioxo napthacene carboxamide is widely used broad-spectrum antibiotics for the treatment of infections. Recently it was found that tetracycline antibiotics have some other important functions. The medicines give new hopes for ailing heart attack (1) and ulcer (2, 3) patients. A novel single tetracycline-regulative adenoviral vector was investigated by Fang group (4) for tumer-specific Bax gene expression and cell killing in vitro and vitro which may become a potential therapeutic agent for the treatment of cancer. The tetracycline hydrochloride-inducible gene expression system has become a commonly used approach to experiments-controlled expression of agents for functional evaluation in mammalian cells (4,5). TC is used to switch gene activity on and off. Researchers can learn more about what specific substances do during different stages of animal's life (7). Knott group (8) investigated tetracycline dependent gave regulation, and reported that trans-regulators yield a variety of expression widows. The structural formula of tetracycline is shown in Fig. 1.
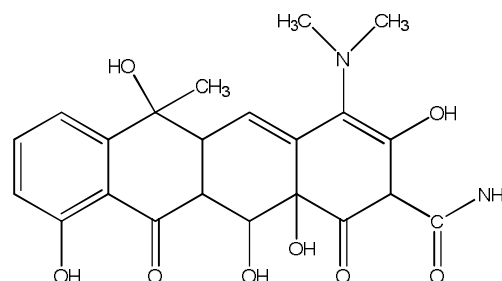


**Fig. 1: Tetracycline (TC)**

Literature survey reveals that there is no report on the kinetics of the oxidation of tetracycline with Bi (V). Such oxidation studies may throw some light on the mechanisms of conversions of the compounds in biological systems. Hence, as a part of my work on mechanistic studies on Bi(V) oxidation of organic and inorganic substrates in general and medicinal compounds in particular (9-13). The aim of this work was investigated the stoichiometry and mechanisms of oxidation of tetracycline by Bi(V) in HClO$_4$-HCl medium.

## 2. EXPERIMENTAL

### 2.1    Materials and Methods

All chemicals used were of reagent grade. Doubly distilled CO$_2$ free water was used throughout the

work. A solution Bi(V) was prepared in 0.01 M $HClO_4$ and 0.01M of HCl mixture. Sodium bismuthate (BDH 85% was used as source of Bi(V). Solutions of tetracycline having molecular formula $C_{22}H_{25}N_2O_8$ were prepared by dissolving an appropriate amount of $CO_2$ free distilled water. $NaClO_4$ and NaOH were employed to maintain ionic strength and pH respectively.

The kinetics of the reaction was investigate in a Julab water bath thermostat at desired temperature (± 0–1°C) at different intervals of time and estimating the iodometrically. The progress of the reaction was followed by measuring the decrease in the absorbance of Bi(V) in the reaction solution in a 1 cm quartz cell of a thermostated compartment of Hitachi model 150-20 spectrophotometer at its absorbance maximum 450 nm, as a function of time where other constituents of the reactions mixture do not absorb significantly. The applicability of Beer's law for Bi(V) at 450 nm under the reaction condition had earlier been verified. Pseudo-first order rate constant $k_{obs}$ were obtained from the slopes of plots of log[Bi(V)] versus time; the plots were linear upto 60% completion of the reaction in acidic medium and the $k_{obs}$ values were reproducible to within ± 5% and deviation from linearization was observed above 60% of reaction due to the retarding effect of one of the product Bi(III). The results are also interpreted in terms of the initial rate of the reaction to avoid the complexities which may arise due to interference by the products. Initial rates were obtained from the tangents at the initial stages of concentration versus time curves by the plane mirror method and were reproducible to within ± 5%. However, the $k_{obs}$ values were used to interpreter the results through the study(15-17).

## RESULTS AND DISCUSSION

3.1    **Stoichiometry** – The stoichiometry of the reaction between Bi(V)    and    tetracycline    was investigated under excess oxidant conditions. The reaction mixtures with different sets of concentrations of reactants were [Bi(V) was in excess over [TC] at a constant ionic strength and acid were kept for 8 h at (25 ± 1)°C in a closed vessel. The remaining Bi(V) was assayed spectrophotometrically by measuring the absorbance at 450 nm. The stoichiometric results indicated that one mole of [TC] consumed one mole of Bi(V).The most probable form of the oxidised product is given as. The product was identified by IR spectra (Fig. 2).The metal----oxygen bonding a t 485cm$^{-1}$

3.2    **[Bi (V)] and [TC] dependence** – the concentrations of Bi(V) and TC were varied in the range $(0.8 – 2.0) \times 10^{-3}$ mol dm$^{-3}$ and $(4.0 – 20.0) \times 10^{-3}$ mol dm$^{-3}$ respectively, at fixed concentration of $HClO_4$ (1.0 mol dm$^{-3}$) and HCl (1.5 mol dm$^{-3}$). The reaction were first order dependence on Bi(V) was in diluted by the linearity of log Bi(V) versus time plots.
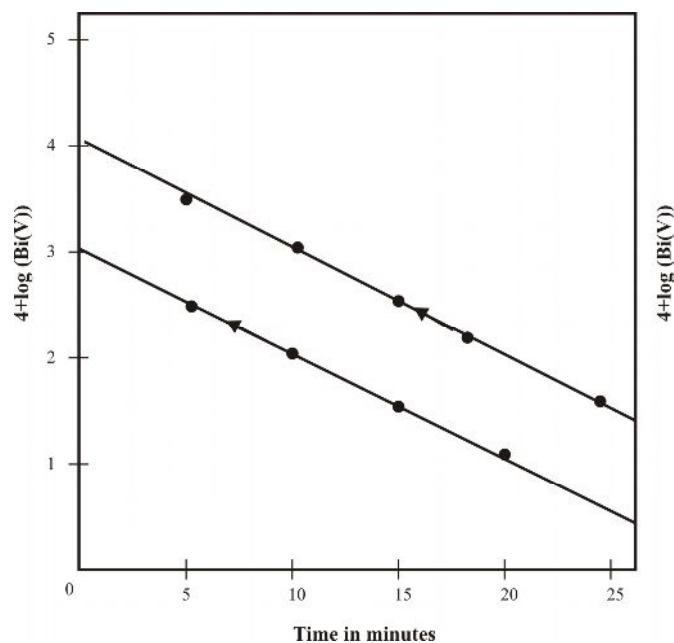


**Fig.2: Plot of 4 + log [Bi(V)] versus time**

pH : 3.0 temperature 303K

3.3    **Hydrogen ion dependence** – The concentration of $HClO_4$ was varied from 0.8 mol dm$^{-3}$ to 2.0 mol dm$^{-3}$ at fixed ionic strength [I = 2.0] adjusted with $NaClO_4$ and at fixed concentration of reactants [Bi(V)] = $1.4\times10^{-3}$ mol dm$^{-3}$ [TC] = $1\times10^{-2}$ mol dm$^{-3}$. The reaction rate remained unchanged.

3.4    **Temperature dependence** – The reaction was carried out at 298, 303 and 308 K at fixed ionic strength, pH and Bi(V). Arrhenius plot of logk versus 1/T gave a straight line. From the slope and intercept, the experimental energy of activation E and the frequency factor were found to be respectively 85.37 KJ mol$^{-1}$ and $4.25 \times 10^{13}$ s$^{-1}$. The Eyring's parameters $\Delta H^*$, $\Delta S^*$ and $\Delta G^*$ which are temperature dependent and can be calculated from

$$\Delta H^* = \Delta E^* - RT$$

$$\Delta S^* = 2.303 \log[Ah/kT]$$

$$\Delta G^* = \Delta H^* - T\Delta S^*$$

The values of $\Delta H^*$, $\Delta S^*$ and $\Delta G+^*$ at 298K obtained respectively 82.89 Kj mol$^{-1}$ 7.987 JK$^{-1}$ 80.51 KJ mol$^{-1}$. The resulting values were $5.26 \times 10^{-3}$, $5.55 \times 10^{-3}$ and $5.80 \times 10^{-3}$ s$^{-1}$ respectively.

3.5    **Effect of ionic strength**: The ionic strength was varied in the range 1.0 – 2.40 by adding requisite quantity of $NaClO_4$ at a fixed concentration of [Bi(V)]: $1.4\times10^{-2}$ mol dm$^{-3}$ [HCl] : 1.50 mol dm$^{-3}$, [$HClO_4$] : 1.0 mol dm$^{-3}$. The reaction rate decreased with the increase in ionic strength indicating reactive species of opposite charge.

3.6     **Effect of Initially Added Product** – The effect of initially added products [TC] and [Bi(V), on the rate of reaction was also studied in the range of $1.0 \times 10^{-3}$ – $1.0 \times 10^{-2}$ mol. dm$^{-3}$ at 25°C at constant [Bi(V)], [TC], [H$^+$] and ionic strength. The added [TC] did not alter the rate of reaction. However [Bi(V)] was shown to have a retarding effect on rate of reaction Table-II.

**Table 1 : Stoichiometric results of oxidation of tetracycline [TC][ wit Bi(V) in HClO$_4^-$ HCl mixture [HClO$_4$] = 1.0 mol dm$^{-3}$, temperature 25°C [HCl] = 1.5 mol dm$^{-3}$**

| [Bi(V)]$\times 10^3$ mol dm$^{-3}$ | [TC] $\times 10^3$ mol dm$^{-3}$ | [Bi(V)]$\times 10^3$ mol dm$^{-3}$ consumed | $\dfrac{\Delta B(V)}{\Delta[TC]}$ |
|---|---|---|---|
| 2.0 | 1.0 | 1.12 | 1.12 |
| 2.10 | 1.0 | 1.33 | 1.13 |
| 2.20 | 1.50 | 1.63 | 1.07 |
| 2.80 | 2.0 | 1.63 | 1.09 |
| 3.1 | 2.3 | 2.30 | 1.17 |
| 3.4 | 2.5 | 2.35 | 1.12 |
| 3.5 | 2.5 | 2.31 | 1.13 |
| 4.0 | 3.0 | 2.65 | 1.15 |
| 4.5 | 3.0 | 2.83 | 1.14 |

**Table 2: Pseudo-first order rate constants of rate oxidation of tetracycline by Bi(V),**

 **temperature 303°K pH : 3.00**

| [Bi(V)]$\times 10^3$ mol dm$^{-3}$ | [TC] $\times 10^3$ mol dm$^{-3}$ | [Bi(V)]$\times 10^3$ mol dm$^{-3}$ | $k_{obs} \times 10^3 s^{-1}$ |
|---|---|---|---|
| 1.00 | 2.1 | 2.0 | 10.2 |
| 2.00 | 2.0 | 2.0 | 12.8 |
| 4.00 | 2.0 | 2.0 | 12.0 |
| 6.3 | 2.0 | 2.0 | 12.5 |
| 2.1 | 2.0 | 2.0 | 3.2 |
| 2.0 | 0.5 | 2.0 | 6.0 |
| 2.0 | 1.0 | 2.0 | 6.0 |

**Assinment of IR of product :** The IR spectra of  of product  show the coordination of Bi(V) with O of TC at the band 425cm$^{-1}$  anf ClO$_4$ bind at  920,931,922, and 962 cm$^{-1}$  .The proposed structure of the complex as follows:
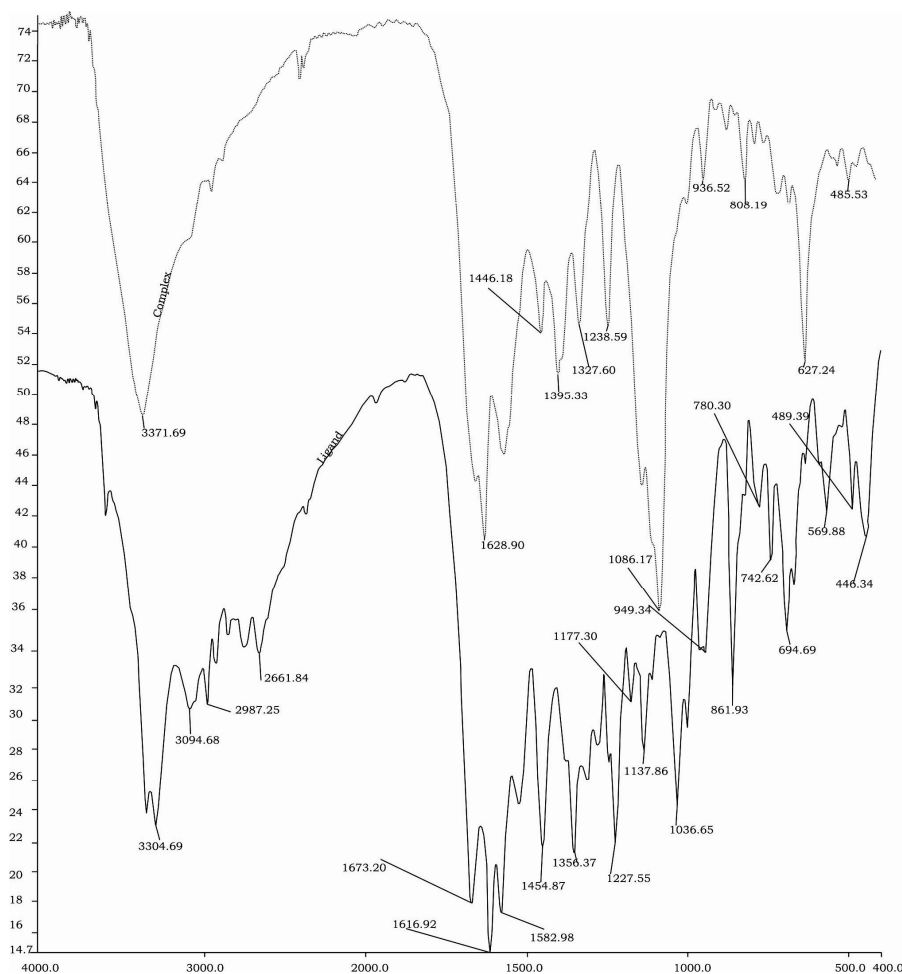


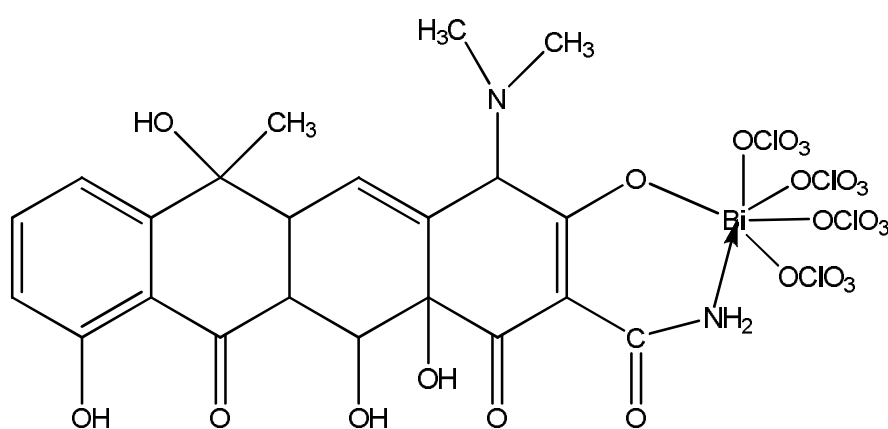**Fig. 3: IR Spectra of ligand-(TC) and complex Bi-TC**



**Figure 4. Proposed   structure of product**

## CONCLUSION

At pH 3, 4- in the presence of heavy metal ions the TC is formed complex series of rearrangements in acidic media. It can be oxidised by Bi (V) in acidic medium. The small value of "k" in the rate determining step proves that the activated complex is more highly ordered than the reactions. This is supported by the large negative value of $\Delta S^*$. The plausible mechanism in conformity with the above experimental facts may be suggested as

$$TC + Bi(V) \rightarrow H_2O \ [Bi .... Tc] + Bi(III)$$
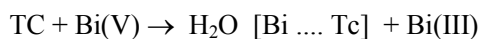
P

Product

where P is the product of the reaction. Under an excess concentration of [Bi (V)] and constant pH, the rate law can be described as follows:

$$V = \frac{d[TC]}{dt} - \frac{d[P]}{dt} - K[TC]^{\alpha}$$

where k′ is a pseudo-first order rate constant and $\alpha$ is the order of the reaction.

Applying the steady state treatment the rate law is derived.

$$-\frac{d[Bi(V)]}{dt} = k[Bi(V)[TC]$$

where k is the first order rate constant. The first order rate calculated at 25°C, $5.26 \times 10^{-3} s^{-1}$.

The thermodynamic parameters were calculated in conventional manner. The low value of $E^*$ and negative value of $\Delta S^*$ suggested that the degree of freedom of intermediate complex is less than that of the reacting molecules and the intermediate complex permits a facile electron transfer from the substrate to Bi(V).

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