Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2019, 8 (3): 1350-1362

(International Peer Reviewed Journal)

Kinetics and Mechanism of Ru(III)-Catalyzed Oxidation of Tetracycline Hydrate by $Cu(Bip)_2^{2+}$ in Alkaline Medium: A Spectrophotometric Studies

Rupam Yadav, Jaya Srivastava, Brijesh Kumar Prajapati, Ranju Pradhan,
Ashok Kumar Singh and Shahla Rahmani*

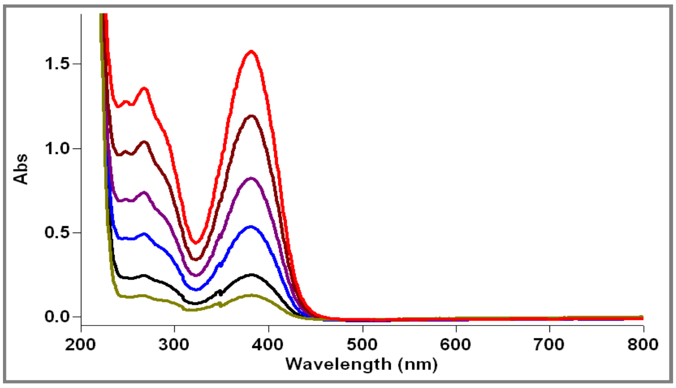
Department of Chemistry, University of Allahabad 211002, **INDIA**
E-mail: ashok_au2@yahoo.co.in

Accepted on 16th April, 2019

ABSTRACT

Kinetic studies in homogeneously Ru(III)-catalyzed oxidation of antibiotics i.e. tetracycline hydrate by copper bipyridyl ($Cu(Bip)_2^{2+}$) *in presence of alkaline medium has been made at* 35^0*C. The reaction exhibits pseudo first-order kinetics with respect to* [$Cu(Bip)_2^{2+}$] *and is first-order with respect to lower [Ru(III)] but tend towards zeroth order at higher [Ru(III)]. The reaction shows first-order kinetics with respect to [Tetracycline hydrate] throughout its variation. The reactions are zero order with respect to both*[OH^-] *and [Bipyridyl]. The rate of the oxidation is unaffected by the change in ionic strength (I) as well as dielectric constant (D) of the medium.* $Cu(Bip)_2^{2+}$*, tetracycline hydrate as such and* [$RuCl_2(H_2O)_3OH$] *have been assumed as the reactive species of Copper bipyridyl, tetracycline hydrate andRu(III) chloride in alkaline medium, respectively. The reaction was studied at four different temperatures and observed values of rate constants were utilized to calculate various activation parameters specially the entropy of activation* ($\Delta S^{\#}$)*. Kinetic studies together with spectral information, activation parameters and multiple regression analysis were made a basis for the formation of reaction mechanism for the catalyzed oxidation of tetracycline hydrate.*

Graphical Abstract



Spectra of tetracycline hydrate solutions recorded at room temperature.

Keywords: Alkaline medium, Catalysis Copper-bipyridyl complex, Spectrophotometric study, Tetracycline hydrate.

INTRODUCTION

Tetracyclines are broad-spectrum antibiotics and exhibited activity against a wide range of microorganisms including gram-positive and gram-negative bacteria, a typical organisms and protozoan parasites [1]. They are known to coordinate to a variety of metal ions [2] and some of these tetracycline-metal complexes are active against resistant bacteria [3].Copper is an essential element for human and most aerobic organisms. Literature shows that copper complexes play important roles in various fields such as catalysis [4], oxidation chemistry [5] and biochemistry [6]. Cu-compounds are expected to be less toxic while retaining effective cytotoxicity towards cancer cells [7]. Literature shows that when Cu(II) as such has been used as an oxidant, the reaction became heterogeneous but when it has been used with complexing agents like tartrate, citrate, picolinate, pyridine, ammonia and bipyridyl, the reaction remained homogeneous. In recent years, the use of transition metal ions such as rhodium, ruthenium, osmium, palladium, manganese, chromium, silver, zirconium and iridium, either alone or as binary mixtures as catalysts in various redox processes have attracted considerable interest [8, 9]. These metals catalyze many oxidation–reduction reactions due to the existence of variable oxidation states, as a consequence of partly filled d or f-orbital. Although the mechanism of catalysts depends upon the nature of main reactant, it has been shown that metal ion act as a catalyst by one of these paths such as the formation of complexes with reactants or oxidation of the substrate itself or through the formation of free radicals. Reports are available in literature regarding the use of Ir(III) [10, 11], Rh(III) [12-14], Ru(III) [15, 16], Pd(II) [17, 18],Pt(IV)[19], Os(VIII)[20-21]and ruthenate ion [22] as homogeneous catalyst in acidic or alkaline medium in various redox processes. Ru(III) is an efficient catalyst in several redox reactions. Currently most promising as future antitumor compounds are complexes based on ruthenium [23]. Earlier kinetics and mechanism of Ru(III)-catalyzed oxidation of some redox reactions have been reported [24-27] In the present study we are reporting the detailed kinetics of Ru(III)-catalyzed oxidation of tetracycline hydrate in alkaline medium with a view to ascertain the reactive species and to find out mechanistic aspects of the reactions. In the present investigation, our main aim was to ascertain whether, the role of tetracycline hydrate in the presence of Ru(III) chloride as catalyst and $Cu(Bip)_2^{2+}$ as an oxidant in alkaline medium is similar to the reported role of tetracycline hydrate in the presence of Rh(III) chloride [28] as catalyst and Ru(III) chloride [29] as an inhibitor .$Cu(Bip)_2^{2+}$as an oxidant in the present study behaves in the same way as it behaved in the reported Rh(III)-catalyzed [28] oxidation of tetracycline hydrate or not? The role of Ru(III) chloride in alkaline medium in the reaction under investigation is also studied. The possibility of formation of a complex between the reactive species of Ru(III) chloride and the reactive species of Cu(II)in alkaline medium and the formation of an activated complex by the interaction of two oppositely charged species are also investigated.

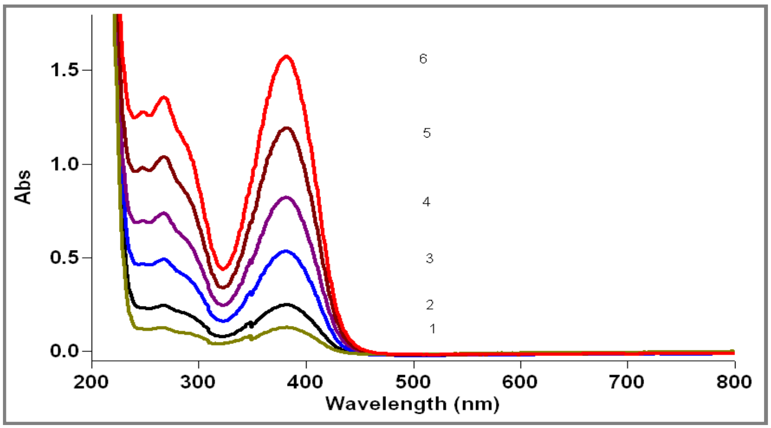
MATERIALS AND METHODS

Method of Study: The study of the reaction rate has been accomplished with the help of Varian Carry Win UV−Vis spectrophotometer connected with a Peltier accessory and computer. The method is based on the difference in light absorbing property of reactants and products. Firstly, absorption spectra were recorded for tetracycline hydrate at 380nm with molar absorptivity 0.1176×10^5 dm ^{3}mol^{-1} cm^{-1} (Figure 1and 2), where the tetracycline hydrates absorbs maximum.

Here the mixture containing the solution of tetracycline hydrate acts as absorbing sample and mixture without tetracycline hydrate acts as reference sample. Decreasing trend of absorbance was recorded with respect to time. The rate of reaction i.e. –dc/dt can be calculated by the help of a plot made between remaining concentration of tetracycline hydrate and time. First-order rate constant was calculated by using the formula,

$$k_1 = -\frac{dc/dt}{[Tc]}$$

Where, Tc represents tetracycline hydrate.



(1)[Tc] = 2.00×10^{-5}M, [Na_2CO_3] = 10.00×10^{-2}M, **(2)**[Tc] = 4.00×10^{-4}M, [Na_2CO_3] = 10.00×10^{-2} M
(3) [Tc] = 6.00×10^{-4}M,[Na_2CO_3] = 10.00×10^{-2} M, **(4)**[Tc] = 10.00×10^{-4} M,[Na_2CO_3] = 10.00×10^{-2}M
(5)[Tc] = 12.00×10^{-4}M[Na_2CO_3] = 10.00×10^{-2}M, **(6)**[Tc] =14.00×10^{-4}M,[Na_2CO_3] = 10.00×10^{-2}M

Figure 1. Spectra of tetracycline hydrate solutions recorded at room temperature

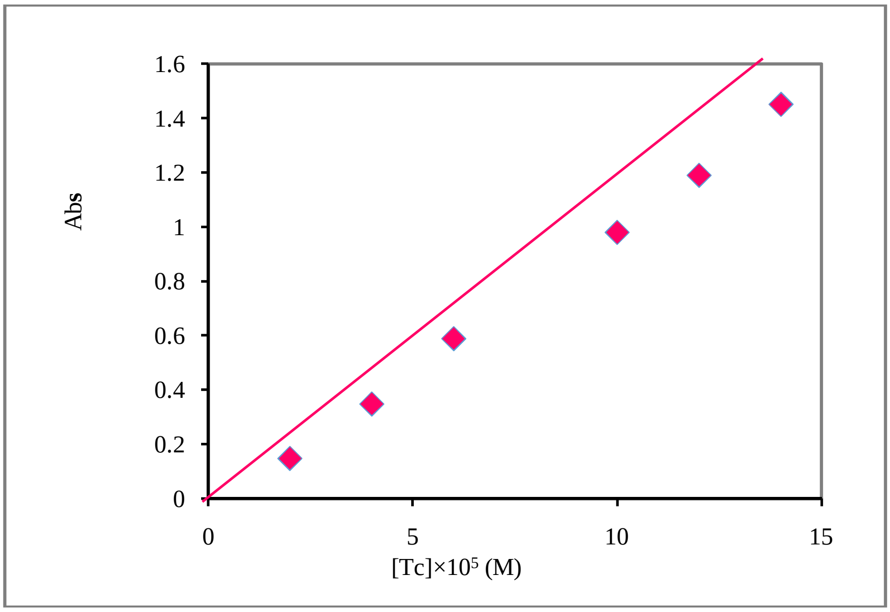
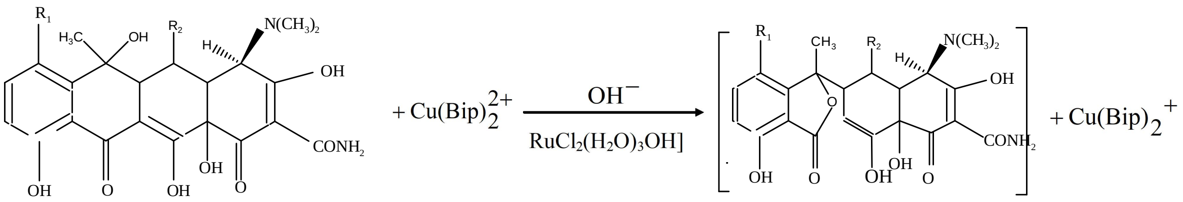
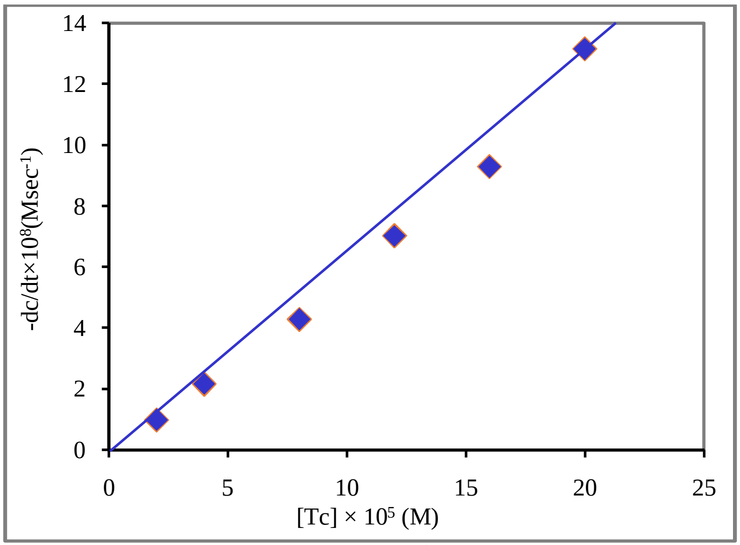


Figure 2 Plot between Absorbance (Abs) and [Tc].

Stoichiometry of the Reactions: In order to find out the total number of moles of oxidant ($Cu(Bip)_2^{2+}$) consumed by one mole of substrate, various sets of reaction mixtures were taken in which concentration of ($Cu(Bip)_2^{2+}$) was in large excess than that of tetracycline hydrate. All the conical flasks containing reaction mixture were allowed to stand for several days at room temperature. Estimation of remaining [$Cu(Bip)_2^{2+}$] showed that one mole of tetracycline hydrate is oxidized by one mole of $Cu(Bip)_2^{2+}$.

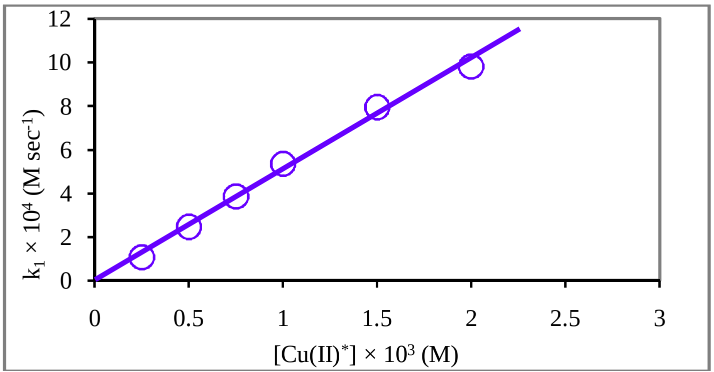


Kinetic Results: To know the effect of tetracycline hydrate on the rate of reaction in its Ru(III)-catalyzed oxidation, a number of kinetic runs were performed by varying [Tc] and keeping the concentration of all other reactants constant at constant temperature and at constant ionic strength. The [Tc] was varied from 2.00×10^{-5}M to 20.00×10^{-5}M. When a plot was made between –dc/dt and [Tc], a straight line passing through origin was obtained (Figure 3). This shows that there is direct proportionality between –dc/dt and [Tc]. On the basis of this, it has been concluded that the order of reaction with respect to [Tc] is unity throughout its ten-fold variation. It is observed that the value of first order rate constant, k_1, increases with increase in $Cu(Bip)_2^{2+}$concentration in the same proportion in which the concentration of $Cu(Bip)_2^{2+}$is increased. This result is further verified by plotting a graph between k_1 and $[Cu(Bip)_2^{2+}]$ (Figure 4), which gives a straight line passing through origin throughout its concentration range. First-order dependence of the reaction on Ru(III) at its lower concentrations tends to zero-order at its higher concentrations(Fig.5). There is no change in pseudo first-order rate constant, k_1, with the change in concentration of $[OH^-]$. The above result shows that the reaction rate is independent of the concentration of OH^-. The pseudo first-order rate constants remain unaffected by the change in bipyridyl concentration. Almost no effect of the ionic strength (I) as well as dielectric constant (D) of the medium on the rate of oxidation was observed in the present investigation. The reaction was studied at four different temperatures (30°, 35°, 40°, and 45°). Increase in temperature increases the velocity of reactions significantly in the oxidation of tetracycline hydrate.



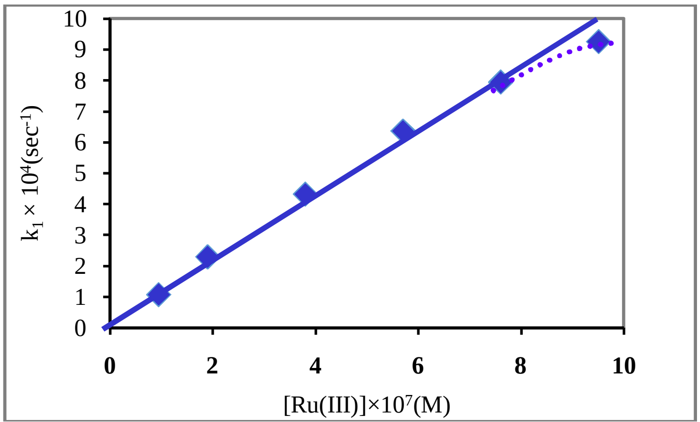
Solution conditions: $[Cu(Bip)_2^{2+}]= 1.00\times10^{-3}$M, [Free Bip] = 60.00×10^{-4}M, $[Ru(III)] = 3.80\times10^{7}$M,$[Na_2CO_3] = 10.00\times10^{-2}$M,$\mu = 10.00\times10^{-1}$M

Figure 3. Plots between –dc/dt and [Tc] at 35°C.



Solution conditions: [Tc] = 8.00×10^{-5}M, [Free Bip] = 60.00×10^{-4}M, $[Ru(III)]=3.80\times10^{-7}$M, $[Na_2CO_3] = 10.00\times10^{-2}$M, $\mu = 10.00\times10^{-1}$M .

Figure 4. Plots between k_1 and $[Cu(II)^*]$ at 35°C.



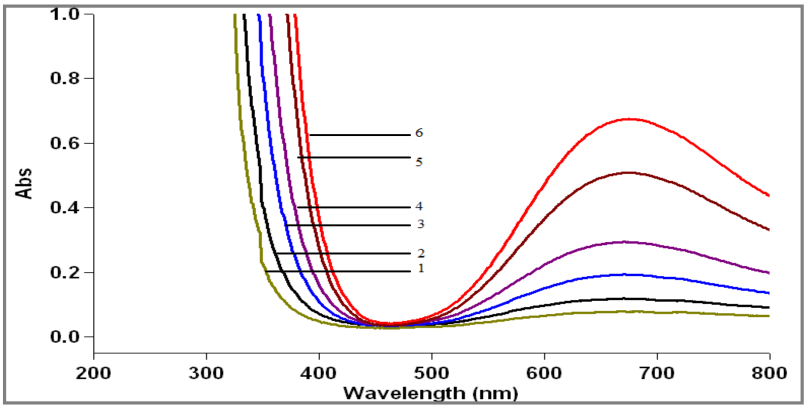
Solution conditions: [Tc] = 8.00×10^{-5}M, [Free Bip] = 60.00×10^{-4}M, [$Cu(Bip)_2^{2+}$]= 1.00×10^{-3}M,[Na_2CO_3]=10.00×10^{-2}M, μ = 10.00×10^{-1}M.

Figure 5. Plot between k_1 and [Ru(III)] at 35°C.

RESULTS AND DISCUSSION

Reactive species of tetracycline hydrate in alkaline medium: Going through the literature [30-33] and making basis to the kinetic observations along with spectral information, it has been concluded that the tetracycline hydrate as such participates in its Ru(III)-catalyzed oxidation by $Cu(Bip)_2^{2+}$ in alkaline medium.

Reactive species of Cu(II) in alkaline medium: In the present study, Cu(II) has been used with bipyridyl as complexing agent in alkaline medium. On the basis of kinetic results obtained and spectroscopic evidence collected, it can be assumed that the reactive species of Cu(II) is $Cu(Bip)_2^{2+}$ instead of free Cu(II). Formation of the complex, $Cu(Bip)_2^{2+}$,is confirmed by its absorption at λ_{max} = 670nm with molar absorptivity $0.59\times10^2 dm^3 mol^{-1} cm^{-1}$ (Fig.6) which is also supported by literature [34].



Solution conditions:
(1) [$Cu(Bip)_2^{2+}$] = 1.00×10^{-3}M, [Free Bip] = 2.00×10^{-3}M, [Na_2CO_3] = 1.00×10^{-2} M
(2)[$Cu(Bip)_2^{2+}$]= 2.00×10^{-3}M, [Free Bip]= 2.00×10^{-3}M, [Na_2CO_3] = 1.00×10^{-2}
(3)[$Cu(Bip)_2^{2+}$] = 4.00×10^{-3} M, [Free Bip] = 2.00×10^{-3}M, [Na_2CO_3] = 1.00×10^{-2}M,
(4)[$Cu(Bip)_2^{2+}$]= 6.00×10^{-3}M, [Free Bip] = 2.00×10^{-3}M, [Na_2CO_3] = 1.00×10^{-2}M
(5)[$Cu(Bip)_2^{2+}$] = 8.00×10^{-3} M, [Free Bip] = 2.00×10^{-3}M, [Na_2CO_3] = 1.00×10^{-2}M
(6)[$Cu(Bip)_2^{2+}$]= 10.00×10^{-3} M, [Free Bip] = 2.00×10^{-3}M, [Na_2CO_3] = 1.00×10^{-2}M

Figure 6. Spectra of $Cu(Bip)_2^{2+}$forsolutions [1-6] recorded at room temperature.

Reactive species of Ru(III) chloride in alkaline medium: Kinetic study of Ru(III)-catalyzed oxidation of 2-methylpentane-2,4-diol by alkaline hexacynoferrate(III) has been made by

A.E.Musientes and co-workes [35] where they have reported that $RuCl_3$ in OH^- range from 10^{-3}M to 0.4M involve the existence of several hydroxo-aquo ruthenium complexes in equilibrium as follows

$$[Ru(H_2O)_6]^{3-} + OH^- \rightleftharpoons [RuCl_2(H_2O)_5OH]^{2+} + H_2O \quad (3)$$

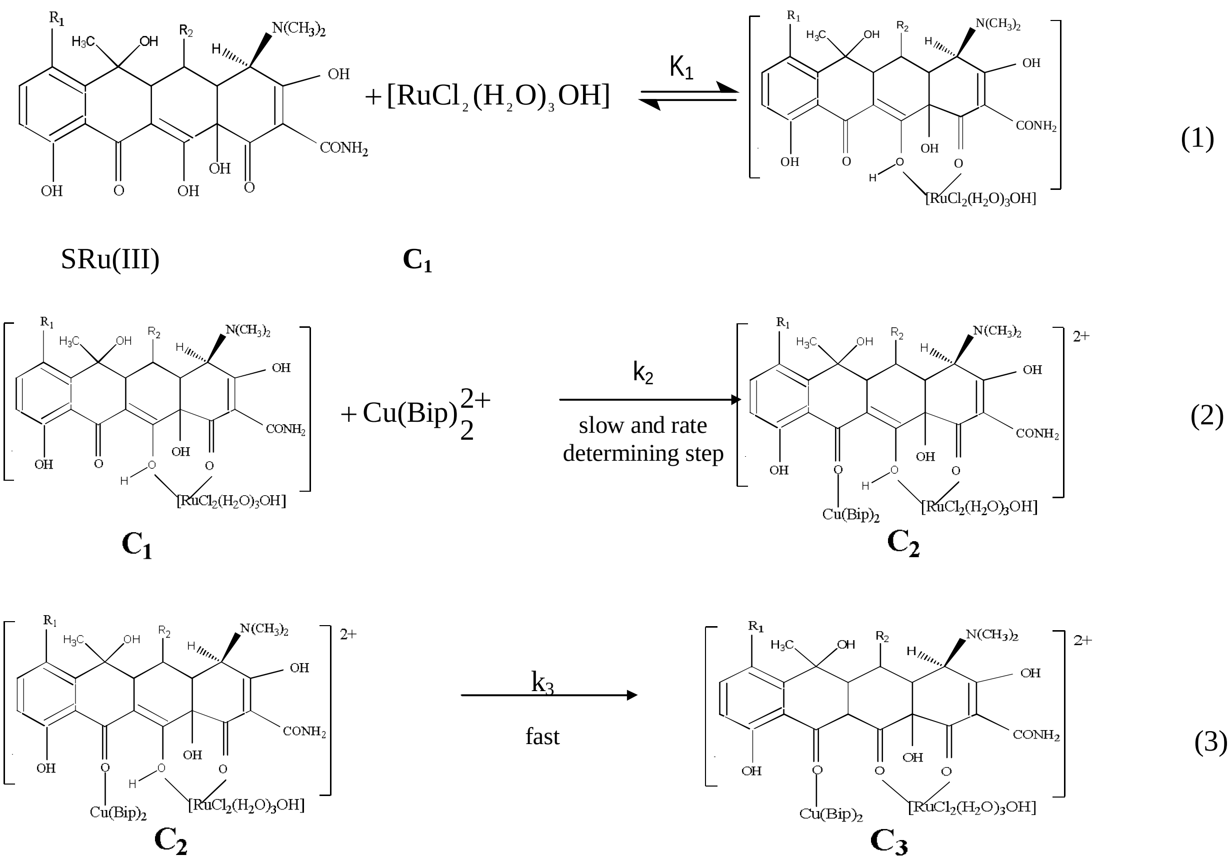
$$[RuCl_2(H_2O)_5OH]^{2+} + OH^- \rightleftharpoons [RuCl_2(H_2O)4(OH)_2]^{+} + H_2O \quad (4)$$

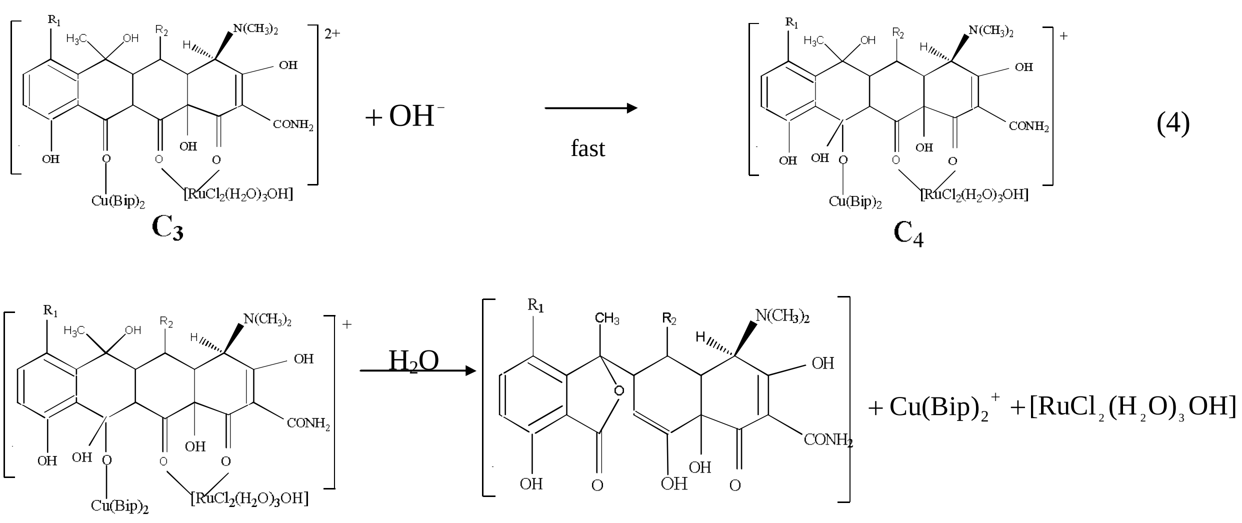
$$[RuCl_2(H_2O)_4(OH)_2]^{+} + OH^- \rightleftharpoons [RuCl_3(H_2O)_3(OH)] + H_2O \quad (5)$$

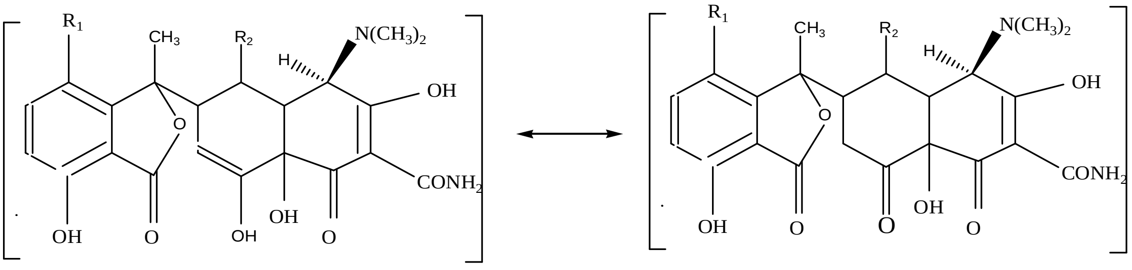
In the present study of oxidation of tetracycline hydrate by Cu(II) complexed with bipyridyl in alkaline medium using Ru(III) as homogeneous catalyst, Ru(III) used in each kinetic run was taken from a solution of Ru(III) chloride prepared in 0.1M HCl (pH=2.0). Considering the facts mentioned above, it can be said that the starting species of Ru(III) chloride is $[RuCl_2(H_2O)_3OH]$ in the present investigation.

Mechanism for the oxidation of tetracycline hydrate by $Cu(Bip)_2^{2+}$ in alkaline medium using Ru(III) chloride as homogeneous catalyst: With the help of the observed kinetic orders with respect to the reactants involved in the reaction, spectrophotometric evidence collected for the formation of reactive complexes and the positive entropy of activation, a most probable reaction mechanism in the form of Reaction Scheme 1 for Ru(III)-catalyzed oxidation of tetracycline hydrate by $Cu(Bip)_2^{2+}$ in alkaline medium can be proposed.

Scheme 1







enol form keto form

According to the aforesaid reaction scheme, the rate in terms of decrease in concentration of tetracycline hydrate can be expressed as

$$\text{rate} = -\frac{d[Tc]}{dt} = k_2[C_1][Cu(II)^*] \qquad (1)$$

On applying the law of chemical equilibrium to steps (I), we have

$$K_1 = \frac{[C_1]}{[S][Ru(III)]} \qquad (2)$$

$$[C_1] = k_2[C_1][Cu(II)^*] \qquad (3)$$

On substituting the value of $[C_1]$ from equation (3) to equation (1), we get

$$\text{rate} = -\frac{d[Tc]}{dt} = k_2K_1[S][Ru(III\ )][Cu(II)^*] \qquad (4)$$

According to the reaction scheme-2, the total concentration of substrate i.e. $[S]_T$ can be expressed as

$$[S]_T = [S] + [C_1] \ (5)$$

On putting the value of $[C_1]$ from equation (3) to equation (5), we have

$$[S]_T = [S] + K_1[S][Ru(III)]$$

Or

$$[S] = \frac{[S]_T}{1 + K_1[Ru(III)]} \qquad (6)$$

With the help of equations (4) and (6), we can write equation (7)

$$rate = -\frac{d[Tc]}{dt} = \frac{k_2 K_1 [S]_T [Ru(III)]\ [Cu(II)^*]}{1 + K_1[Ru(III)]} \qquad (7)$$

Equation (7) is the final rate law which is strictly in accordance with our experimental findings where unity orders in [S] and $[Cu(II)^*]$ and fractional positive order in [Ru(III)] was obtained.

On reversing equation (7)

$$\frac{1}{rate} = \frac{1}{K_1 k_2 [S]_T [Cu(II)^*][Ru(III)]} + \frac{1}{k_2 [S]_T [Cu(II)^*]} \qquad (8)$$

Equation (8) can also be written as equations (9)

$$\frac{[S]_T[Cu(II)^*]}{rate} = \frac{1}{K_1 k_2 [Ru(III)]} + \frac{1}{k_2} \qquad (9)$$

Equations (9) shows that if a plot is made between $\frac{[S]_T[Cu(II)^*]}{Rate}$ vs. $\frac{1}{[Ru(III)]}$ **,** a straight line having

an intercept on y-axis will be obtained. When plots between $\frac{[S]_T[Cu(II)^*]}{Rate}$ and $\frac{1}{[Ru(III)]}$ was made**,** the straight line having intercepts on y-axis was obtained (Figure 7). This proves the validity of rate law (7) and hence the proposed reaction scheme 1. From the intercept and slope, the values of constants K_1 and k_2 were calculated and found as 1.80×10^6 $mol^{-1}dm^3$, 1.50 $mol^{-1}dm^3sec^{-1}$ respectively. Utilizing these values of the rate constants the rates for the variation of [Ru(III)] was calculated and are presented in table 1. From a perusal of table 1, it is quite evident that there is a close similarity between the observed rates and the calculated rates. This further proves the validity of rate law (7) and hence the proposed mechanism.

Multiple Regressions: Experimental kinetic data for the variation of $[Cu(II)^*]$ and [Ru(III)] were analyzed for Multiple Regression Analysis. The results of fitting a multiple linear regression model to have been used to calculate rates for variation of $[Cu(II)^*]$ and [Ru(III)] and it was found that the rate calculated on the basis of equation of fitted model are in close agreement with the observed rates and the rates calculated on the basis of rate law (7) (Table 1). This gives support to the proposed rate law and suggested mechanism. The equation of the fitted model is

$$Col\_1 = 5.81695 + 0.921236 * Col\_2 + 0.8501 * Col\_3$$

Where Col_1 = ln k_1, Col_2 = ln $[Cu(II)^*]$ and Col_3 = ln [Ru(III)]

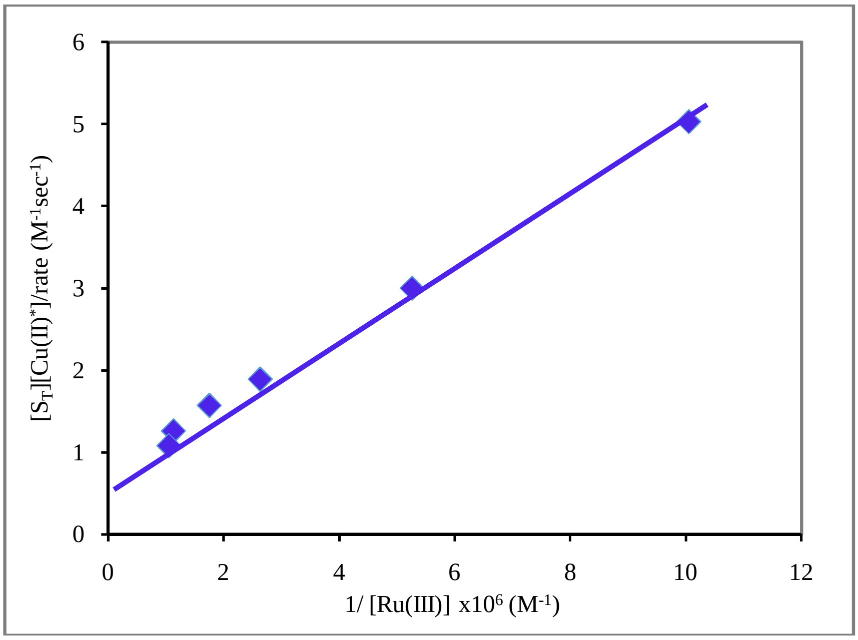


Figure 7. Plot between $[S]_T$/Rate and 1/[Rh(III)] at 35°C.

Table 1. Experimental and calculated values of the rate for the variations of $[Cu(II)^*]$, and [Ru(III)] in the Ru(III)-catalyzed oxidation of tetracycline hydrate by $Cu(Bip)_2^{2+}$ at 35°C.

$[Cu(II)^*]$ × 10^3 (M)	[Ru(III)] ×10^7 (M)	-dc/dt×10^8($Msec^{-1}$)		Rate calculated on the basis of Multiple Regression Analysis
		Experimental rate	Rate calculated on the basis of rate law (equation(7))	
0.25	3.80	0.86	0.76	0.82
0.50	3.80	1.97	1.77	1.49
0.75	3.80	2.40	2.35	2.11
1.00	3.80	4.28	4.30	2.70
1.50	3.80	5.10	5.18	3.82
2.00	3.80	6.36	6.42	4.90
2.50	3.80	7.90	8.12	5.94
1.00	0.95	1.59	1.67	1.70
1.00	1.90	2.67	2.90	2.70
1.00	3.80	4.23	4.63	4.30
1.00	5.70	5.10	5.77	5.64
1.00	7.60	6.36	6.58	6.84
1.00	9.50	7.41	7.19	7.94

Solutions conditions: [Tc] = 8.00×10^{-5}M, $[Na_2CO_3]$ = 10.00×10^{-2} M,[Free Bip] = 6.00×10^{-3} M, μ = 1.70M

With the help of pseudo first-order rate constants at four different temperatures the energy of activation and other activation parameters have been calculated and are presented in tables 2.

Table 2. Activation parameters for the oxidation of tetracycline by $Cu(Bip)_2^{2+}$ using Ru(III) chloride as homogeneous catalyst in alkaline medium at 35^0C

Reducing substrate	k_r ($mol^{-2}dm^6 sec^{-1}$)	$\Delta H^\#$ ($kJ\ mol^{-1}$)	$\Delta G^\#$ ($kJ\ mol^{-1}$)	$\Delta S^\#$ (eu)	A ($mol^{-3}dm^9 sec^{-1}$)
Tetracycline hydrate	1.10×10^6	68.88	38.98	23.13	1.10×10^{18}

It is also reported [36] that when reaction occurs between an ion and a neutral molecule, the transition state becomes less polar than the initial state, because in the transition state the same charge is dispersed over a greater volume. In the present investigation, observed positive entropy of activation in the oxidation of tetracycline hydrate clearly supports the interaction between complex, C_1, and species $Cu(Bip)_2^{2+}$in the rate determining step leading to the formation of a less polar activated complex, C_2, which ultimately converts into products via several fast steps of the proposed reaction scheme 1.

Comparative studies: The findings of the present study of oxidation of tetracycline hydrate by $Cu(Bip)_2^{2+}$in presence of Ru(III) as homogeneous catalyst have been compared with the results reported for Rh(III) catalyzed [28] oxidation of tetracycline and oxidation of lactose by $Cu(Bip)_2^{2+}$using Ru(III) chloride [29] as an inhibitor in alkaline medium. When the present study has been made for the effect of [Cu(II)*] on the rate of oxidation, it is found that the rate is directly proportional to [Cu(II)*]. Contrary to this, the first to zero order kinetics in [Cu(II)*] was observed for Rh(III)-catalyzed [28] oxidation and no effect of [Cu(II)*] on the rate of reaction was found for Ru(III) catalyzed [29]oxidation. In the present study first-order kinetics tends towards zero order with respect to [Ru(III)] has been observed throughout its variation. This result is similar to the reported fractional positive order kinetics with respect to [Rh(III)] [28]. It is also contrary to the role of Ru(III) [29] as an inhibitor in the oxidation of lactose by $Cu(Bip)_2^{2+}$ in alkaline medium. On the basis of observed kinetic data and spectroscopic evidence, it has been assumed that the species $[RuCl_2(H_2O)_3OH]^-$ is the reactive species of Ru(III)-chloride in the oxidation of tetracycline hydrate, whereas $[RhCl_3(H_2O)_2(OH)]^{2-}$ is found as reactive species of Rh(III)-chloride in the oxidation of tetracycline [28] and $[RuCl_2(H_2O)_2(OH)_2]^-$ as the reactive species of Ru(III)-chloride [29] in the oxidation of lactose by $Cu(Bip)_2^{2+}$in alkaline medium. Zero order kinetics in $[OH^-]$ in the present study is similar to the zero-order kinetics of $[OH^-]$ in the Rh(III)-catalyzed [28] oxidation and contrary to second-order kinetics tending towards first-order kinetics in the oxidation of lactose using Ru(III) as an inhibitor [29]. There is no effect of dielectric constant of the medium on the rate of reaction in the present study as well as in the reported [28] oxidation of tetracycline hydrate by $Cu(Bip)_2^{2+}$in alkaline medium using Rh(III) as catalyst. This result is contrary to the result observed in the oxidation of lactose by $Cu(Bip)_2^{2+}$in alkaline medium using Ru(III) as an inhibitor [29] where it is concluded that there is increase in first-order rate constant k_1 with the decrease in dielectric constant of the medium. In view of the facts mentioned above, it can be said that the present study is different in many respect from the other two studies reported earlier.

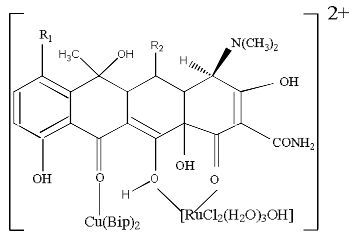
APPLICATION

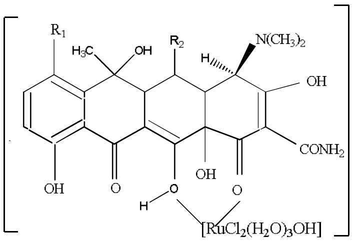
Majority of the commonly used antibiotics fall into following groups: DNA damage causing agents, inhibitors of protein synthesis, inhibitors of cell wall biosynthesis and metabolic inhibitors. Therefore knowledge about molecular mechanism of antibiotic action, related bacterial response and factors modulating antibiotic activity could be of used for development of improved antibacterial substances and therapeutic regimen, which could help us in keeping pace with remarkable adaptability of bacteria. The oxidation of tetracycline hydrate has been studied in detail by using copper bipyridyl as oxidant in alkaline/acidic medium using Ru(III) chloride as catalyst.

CONCLUSION

The following conclusions can be derived from the observed kinetic data and spectral information collected for the Ru(III)-catalyzed oxidation of tetracycline by $Cu(Bip)_2^{2+}$ in alkaline medium:

1. $Cu(Bip)_2^{2+}$ and tetracycline hydrate as such have been assumed as the reactive species of $Cu(II)^*$ and tetracycline hydrate in alkaline medium, respectively.
2. $[RuCl_2(H_2O)_3OH]$ are reactive species of Ru(III) chloride in alkaline medium.
3. First-order kinetics with respect to $[Cu(II)^*]$ throughout its variation has been observed.

4. The complex, 

has been proposed as the most reactive activated complex in the Ru(III)-catalyzed oxidation of tetracycline by Cu(Bip)$_2^{2+}$ in alkaline medium.
5. In step (II) of reaction scheme-2, in which the interaction between a charged species, Cu(Bip)$_2^{2+}$and a natural molecule 

results in the formation of an activated complex, is supported by the observed positive entropy of activation.
6. The rate of oxidation of Ru(III)-catalyzed oxidation of tetracycline hydrate is unaffected by the ionic strength of the medium.

REFERENCES

[1]. I. Chopra, M. Robert, Tetracycline Antibiotics: Mode of Action, Applications, Molecular Biology, and Epidemiology of Bacterial Resistance, *Microbiol. Mol. Biol. Rev.*, **2001**, 65(2), 232.

[2]. G. J. Palm, T. Lederer, P. Orth, W. Saenger, M. Takahashi, W. Hillen, W. Hinrichs, Specific Binding of Divalent Metal Ions to Tetracycline and to the Tet repressor/Tetracycline Complex, *J. Biol. Inorg. Chem.*, **2008**, 13, 1097.

[3]. E. C. Souza, T. L. Loyola, M. B. Rodriguez, M. A. Menezes, B. C. Menezes, N. A. Rey, E. C. P. Maia, Synthesis and Characterization of a Tetracycline-platinum(II) Complex Active Against Resistant Bacteria, *J. Inorg. Biochem.*, **2005**, 99, 1001.

[4]. J. Chen, P. Sun, Y. Zhang, C. H. Huang, Multiple roles of Cu(II) in catalyzing hydrolysis and oxidation of β-lactam antibiotics, *Environ. Sci. Technol.*, **2016**, 50, 12156−12165.

[5]. A. K. Singh, M. Singh, J. Srivastava, S. Rahmani, The kinetics of Rh(III)-catalyzed oxidation of D(+) melibiose by Cu(II) bipyridyl complex in alkaline medium, *J. Applicable Chem.*, **2015**, 4(2), 510-524.

[6]. I. Iakovidis, I. Delimaris, S. M. Piperakis, Copper and Its Complexes in Medicine: A Biochemical Approach, *Approach. Mol. Bio. Int.*, **2011**, 494-529

[7]. C. Marzano, M. Pellei, F. Tisato, C. Santini, Copper complexes as anticancer agents, Anti Cancer Agents, *Med. Chem.*, **2009**, 9, 185–211.

[8]. A. K. Das, Kinetic and mechanistic aspects of metal ion catalysis in cerium(IV) oxidation, *Coord. Chem. Rev.*, **2001**, 213, 307-325.

[9]. H. B. Asghar, H. M. Altass, A. Fawzy, Transition metal-catalyzed oxidation of L-asparagine by platinum(IV) in acid medium: a kinetic and mechanistic study, *Transit. Met. Chem.*, **2015**, 40, 587–594.

[10]. A. K. Singh, P. Singh, J. Srivastava, Sh. Rahmani, R. Srivastava, Sh. Srivastava, R. S. Bala, Kinetics of Ir(III)-Catalysed Oxidation of D-Xyloseby Sodium Metaperiodate in Alkaline Medium, *Oxidation Communications*, **2015**, 38(4), 1547–1561.

[11]. B. K. Prajapati, J. Srivastava, R. Pradhan, S. K. Singh, A. K. Singh, S. Rahmani, Kinetics and Mechanism of Ir(III)-Catalyzed Oxidation of D-Galactose by Potassium Iodate in Aqueous Alkaline Medium, *J. Applicable Chem.*, **2017**, 6(6), 1158-1170.

[12]. A. K. Singh, R. K. Singh, J. Srivastava, S. Rahmani, S. Yadav, Kinetic and mechanistic studies of oxidation of glycine and valine by N-bromosuccinimide using chloro complex of Rh(III) in its nano-concentration range as homogeneous catalyst, *Ind. J. Chem*., **2012**, 51A, 681-689.

[13]. A. K. Singh, R. Pradhan, J. Srivastava, B. K. Prajapati and S. Rahmani, Kinetic Studies of Rh (III)-Catalysed Oxidation of Mannose by N-Bromoacetamide in Alkaline Medium, *J. Applicable Chem*., **2017**, 6(5), 923-933.

[14]. A. K. Singh, R. Singh, J. Srivastava, S. Rahmani, S. Srivastava, Mechanistic studies of oxidation of maltose and lactose by $[H_2OBr]^+$ in presence of chloro-complex of Rh(III) as homogeneous catalyst, *J. Organomet. Chem*., **2007**, 692, 4270–4280.

[15]. A. K. Singh, V. K. Singh, S. Kumari, S. Kumar, V. Singh, J. Srivastava, S. Rahmani,Mechanistic Studies of Ru(III) Chloride Catalyzed Oxidation of Lactose by Sodium Metaperiodate in Alkaline Medium, *J. Applicable Chem*., **2018**, 7 (2), 403-411.

[16]. A. F. Ishaq, A. Zaafarany, K. S. Khairou, S. S. Ashour, N. Yarkandi, Kinetics and Mechanism of Palladium(II)-Catalyzed Oxidation of Inositol by Hexachloroplatinate(IV) in Perchlorate Solutions,American, *J. Applied Chem*., **2016**, 5(4), 185-191.

[17]. A. Fawzy, I. A. Zaafarany, F. Turkistani, J. Alfahemi, M. Morad, Palladium(II)-Catalyzed Oxidation of Pyrimidine Derivative by Hexacyanoferrate(III) in Aqueous Alkaline Medium: A Kinetic Study, *American Journal of Chemical Engineering*, **2016**, 4(2), 38-45.

[18]. A. K. Singh, R. Prakash, J. Srivastava, S. Kumar, S. K. Singh, S. Rahmani, Kinetics and Mechanism of Pd (II) Chloride Catalyzed Oxidation of L-Proline by N-Chlorosuccinimide in Acidic Medium, *J. Applicable Chem.*, **2017**, 6(4), 513-525.

[19]. R. Tripathi, S. K. Upadhyay, Kinetics of oxidation of reducing sugars by catalytic amount of osmium(VIII) in presence of periodate, *Int. J. Chem. Kinet*., **2004**, 36, 441-448.

[20]. A. A. P. Khan, A. Khan, A. M. Asiri, N. Azum, M. A. Rub, M. M. Rahman S. B. Khan, Mechanistic Investigation of Osmium(VIII) Catalyzed Oxidation of Glutamic Acid With Sodium Salt of N-Chloro 4-Methylbenzenesulfonamide in Aqueous Media: A Practical Approach, Synthesis and Reactivity in Inorganic, M*etal-Organic and Nano-Metal Chemistry*, **2016**, 1, 46

[21]. V. Devra, M. B. Yadav, Kinetics and mechanism of osmium (VIII) catalyzed oxidation of valine by hexacyanoferrate (III) in alkaline medium, *Rasayan J.Chem*, **2012**, 5(1), 67-73.

[22]. A. K. Singh, N. Chaurasia, S. Rahmani, J. Srivastava, A. K. Singh,Ruthenate ion catalysed oxidation of D- galactose and D- xylose by alkaline solution of sodium metaperiodate- A kinetic study, *J. Chem. Res*., **2005**, 304-310.

[23]. R. Trondl, P. Heffeter, C. R. Kowol, M. A. Jakupec, W. Berger, B. K. Keppler,The first Ruthenium based anticancer drug on the edge to clinical application, *Chem. Sci*., **2014**, 5, 2925-2932.

[24]. A. K. Singh, R. Singh, J. Srivastava, S. Rahmani, R. Pradhan, A Kinetic Approach for $(H_2OBr)^+$ Oxidation of Glucose in Presence of $[RhCl_4(H_2O)_2]^-$ as Catalyst, *J. Applicable Chem.*, **2015**, 4(2), 587-600.

[25]. A. K. Singh, M. Singh, J. Srivastava, S. Rahmani, R. Yadav, Kinetics of Rh(III)-catalyzed Oxidation of D(+) melibiose by Cu(II)-bipyridyl Complex in Alkaline Medium, *J. Applicable Chem*., **2015**, 4(2), 510-524.

[26]. A. K. Singh, P. Singh, J. Srivastava, S. Rahmani, S. K. Singh, Catalytic Performance of $RhCl_3(H_2O)_3$ in its Nano-concentration Range in the Kinetic Studies of Oxidation of D-glucose and D-fructose by Protonated N-bromosuccinimide, *Journal of Energy and Chemical Engineering*, **2014,** 2(1), 8.

[27]. A. K. Singh, R. Srivastava, S. Srivastava, J. Srivastava, S. Rahmani, B. Singh, N-Bromosuccinimide Oxidation of Maltose and D-galactose Using Chloro-complex of Rh(III) in its Nano-concentration Range as Homogeneous Catalyst: A Kinetic and Mechanistic Study, *J. Mol. Cat A: Chem*, **2009**, 64, 310. Add end page number

[28]. A. K. Singh, R. Yadav, J. Srivastava, R. S. Bala, R. Pradhan, S. Rahmani, Kinetics of Rh(III)-catalysed Oxidation of Tetracycline Hydrate by Cu(II) Complexed with Bipyridyl in Alkaline Medium: a Spectrophotometric Study, Oxidation Communications, 2017, 40(4), 1311-1328.

[29]. A. K. Singh, M. Singh, J. Srivastava , S. Rahmani, Role of Ru(III) as an inhibitor in oxidation of lactose by $[Cu(Bip)_2]_2^+$ in alkaline medium: Spectrophotometric and kinetic studies, *Indian Journal of Chemistry,* **2013**, 52A, 599-607.

[30]. W. R. Chen, C. H. Haung, Transformation of tetracyclines mediated by Mn(II) and Cu(II) ions in the presence of oxygen, *Enviorn. Sci. technol.*, **2009**, 43, 401-407.

[31]. M. J. Bojcauk, L. Lambs, H. Kozlowski, G. Berthon, *Inorg. Chem*., 1993, 32, 428-437.

[32]. Y. Chen, C. Hu, J. Qu, M. Yang, Photodegradation of tetracycline and formation of reactive oxygen species in aqueous tetracycline solution under simulated sunlight irradiation, *J. Photochemistry and Photobiology A: Chem.,* **2008**, 197, 81-87.

[33]. A. K. Singh, M. Singh, S. Rahmani, J. Srivastava, J. Singh, Kinetics of the Oxidation of Tetracycline Hydrate by Copper(II) Complexed with Bipyridyl in Alkaline Medium Using Chloro-complex of Palladium(II) as Homogeneous Catalyst, *Ind. Eng. Chem. Res*., **2012**, 51, 5728.

[34]. E. Prenesti, P. G. Daniele, S. Berto and S. Toso, Spectrum–structure correlation for visible absorption spectra of copper(II) complexes showing axial co-ordination in aqueous solution, *Polyhedr.,* **2006**, 25, 2815-2823.

[35]. A. E. Mucients, F. J. Poblete, R. E. Gabaldon, M. A. Rodriguez, F. Santiago, *J. Chem. Res.(S),* **1998**, 286-287.

[36]. K. A. Connors, Reaction Mechanisms in Organic Analytical Chemistry. A Wiley-Inter science Publication, New York, **1973**, 74–75.