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Mechanistic studies of Ru(III) catalyzed oxidation of antibiotic drug chloramphenicol by chloramine –T in $HClO_4$ medium

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ABSTRACT

The kinetics of oxidation of chloramphenicol by chloramine-T has been investigated over the temperature range of 308-328 K. The reaction has been found to proceed quantitatively over a wide range of experimental conditions. Oxidation of antibiotic involves four electron changes and the product of oxidation has been identified. Oxidation of antibiotic exhibits first order kinetics w.r.t [CAT]. The rate of reaction was found to be independent of the concentration of the substrate. The fractional order dependence of rate on $[H^+]$ *suggests complex formation b/w CAT and* $[H^+]$*. The rate of reaction was found to be first order w.r.t. Ru(III) also. Thermodynamic parameters were evaluated. A suitable reaction scheme is proposed and appropriate rate law is derived to account for the observed kinetic data.*

Keywords- *Chloramphenicol, Chloramine-T, Thermodynamic parameters, Ruthenium (III) catalysis*

INTRODUCTION

Transition metals are known to catalyze many redox reactions due to multiple oxidation states. Transition metals and their higher oxidation states can be generally stabilized with unstable polydentate ligands. A great interest has been shown in using transition metals such as ruthenium, osmium, palladium and iridium either alone or as binary mixtures [1].

Ruthenium (III) acts as a homogenous catalyst in the oxidation of many organic and inorganic substrates [2,3]. The unanalyzed reaction of oxidation of chloramphenicol and ruthenium(III) catalyzed reaction has been studied[4,5]. Ruthenium catalysis in redox reactions involves different degrees of complexity, due to formation of different intermediate complexes and different oxidation states of ruthenium.

Chloramphenicol (CAP) is effective against a wide variety of gram positive and gram negative bacteria, including mostly anaerobic microorganisms. It is the first broad spectrum antibiotic drug, has been analyzed by spectrophotometric, polarographic, GLC, and HPLC techniques [6-11]. Chloramphenicol undergoes hydrolysis in strong acidic and basic media at elevated temperature [12-13].

Aromatic sulphonyl monohaloamines have been used as versatile oxidizing agents [14-15]. Oxidimetric estimation of chloramphenicol has been studied with aromatic sulphonyl monohaloamines [16] but no information has been found for its oxidation using ruthenium (III) as catalyst. Hence, the present investigation aimed to establish the reactivity of chloramphenicol towards chloramines-T in ruthenium (III) catalyzed reactions and to arrive at a plausible mechanism.

MATERIALS AND METHODS

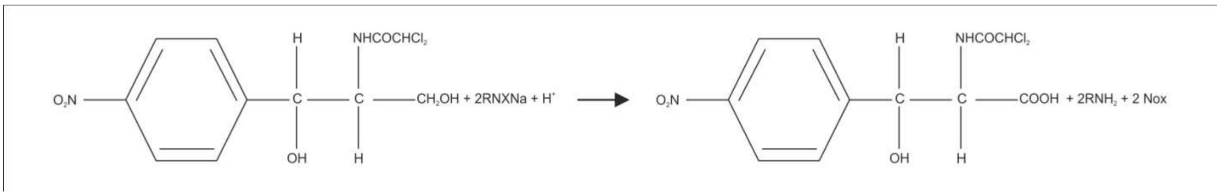
A solution of CP (S.D. Fine Chemicals) was prepared by dissolving an appropriate amount in double distilled water. The purity was checked by its melting point i.e. 151^{0}C (literature- 149-153^{0}C). Analytical grade chemicals and double distilled water was used throughout the studies. CAT was purified by the method of Morris et al [16]. The oxidation of CP by CAT in the presence of Ru (III) catalyst was studied at 308 K. The reaction was initiated by mixing CAT with CP solution which also contained required concentrations of $HClO_4$, KCl, Hg $(OAc)_2$ and ruthenium (III) as catalyst.

The progress of the reaction was monitored iodometrically under suitable and desirable reaction conditions. The course of reaction was studied for at least up to seventy percent completion of the reaction. The oxidation of CP with CAT is not feasible at pH 1-10. The oxidation was also very slow in aqueous solution and became appreciable only in presence of H^+ ions at higher temperature [17]. Hence, detailed kinetic investigations of oxidation of CP by CAT were made in perchloric acid medium using ruthenium (III) as catalyst.

RESULTS AND DISCUSSION

Stoichiometry and product analysis

Different sets of the reaction mixture in perchloric acid medium (with excess of CAT) were kept for over 48 hrs at 313K, keeping other conditions constant. The determination of unconsumed CAT in the reaction mixture showed that 1 mole of CP consumed 2 moles of CAT. The observed Stoichiometry is shown as-



After completion of the reaction, the reaction mixture was acidified, concentrated and extracted with ether. The ether layer was subjected to column chromatography and various fractions were used for spectral investigations [18]. From the IR and UV spectra, the main oxidation product was identified and confirmed.

Reaction orders

The reaction orders have been determined by varying the concentrations of CP, CAT, H+, Ruthenium, in turn by keeping the others constant.

Dependence on [substrate]

The effect of CP was studied by varying it in the concentration range of 1.0 x 10^{-3}- 10.00 x 10^{-3} mol dm^{-3} keeping all other conditions and variable constant. The value of kr remained constant (table-1) indicating zero order dependence of the reaction on [CP].

Dependence on oxidant

The oxidation concentration was varied in the range of 1.0 x 10^{-3}- 8.00 x 10^{-3} .The fairly constant value of K indicates the order with respect to CAT was unity in Ru(III) catalyzed reactions. (Supporting information, (table- 1).

Dependence on [ruthenium (III)]

The catalyst concentration was varied in the range of 1.0 x 10^{-6}- 10.00 x 10^{-6}. The rate of reaction increased with increase in concentration of Ru (III) confirming first order dependence on it (table-1), (figure-1).

Effect of ionic strength on the rate

The ionic strength of the medium was varied by the addition of $NaClO_4$ (0.1 – 0.5 mol dm-3). The rate of reaction was not changed confirming the involvement of non ionic species in the rate limiting step.

Table 1. Effect of varying oxidant, chloramphenicol, Ru(III), $HClO_4$ concentrations on the reaction rate at 308K in aqueous acidic medium

[CAT] x 10^3 / mol dm^{-3}	[CP] x 10^3 / mol dm^{-3}	[Ru] x 10^6 / mol dm^{-3}	[H^+] x 10^3 / mol dm^{-3}	kr x 10^4 /s^{-1}	Kc x 10^4 /s^{-1}
0.50	1.00	3.00	0.50	2.40	1.99
1.00	1.00	3.00	0.50	2.32	2.20
2.00	1.00	3.00	0.50	2.28	1.97
4.00	1.00	3.00	0.50	2.27	2.31
6.00	1.00	3.00	0.50	2.30	2.00
8.00	1.00	3.00	0.50	2.10	1.98
2.00	1.20	3.00	0.50	3.11	3.05
2.00	2.00	3.00	0.50	2.90	3.10
2.00	4.00	3.00	0.50	2.98	3.00
2.00	6.00	3.00	0.50	3.19	2.99
2.00	8.00	3.00	0.50	3.40	3.20
2.00	10.0	3.00	0.50	3.00	2.98
2.00	1.00	1.00	0.50	1.50	1.20
2.00	1.00	2.00	0.50	2.20	2.30
2.00	1.00	4.00	0.50	3.92	4.00
2.00	1.00	6.00	0.50	5.71	5.50
2.00	1.00	8.00	0.50	6.70	6.93
2.00	1.00	10.0	0.50	11.9	12.9
2.00	1.00	3.00	0.10	0.67	0.60
2.00	1.00	3.00	0.25	0.93	0.74
2.00	1.00	3.00	0.50	1.50	1.39
2.00	1.00	3.00	1.00	2.45	2.31
2.00	1.00	3.00	1.50	3.20	2.90
2.00	1.00	3.00	2.00	3.30	3.50

Effect of dielectric constant on the rate

Effect of dielectric constant was studied by varying ethanol and water percentage. Experimentally no significant was observed on the rate of reaction [19].

Effect of the product PTS concentration on the rate

The addition of PTS (1x10^{-3}-10x10^{-3} mol dm^{-3}), the reduced product of oxidant CAT had no significant effect on the rate. This indicates the non involvement of it in pre-equilibrium step.

Figure-1

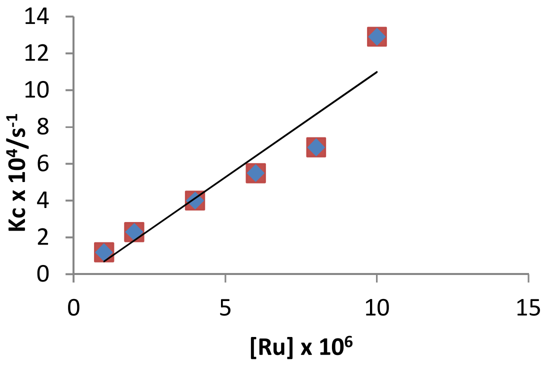
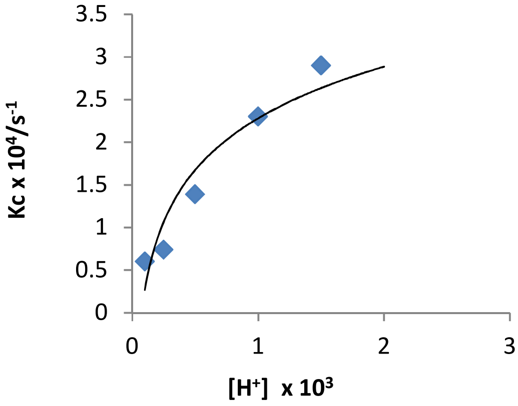


figure-2



Effect of halide ions on the rate

Reactions were studied by adding $NaClO_4$ (1x10^{-3}-10x10^{-3} mol dm^{-3}). The rate remain unchanged with added Cl^- indicates that their effect is not significant on the rate of reaction.

Effect of acid on the rate

The effect of H^+ ions was studied by variation in its concentrations (table-1). The rate constant increased with increase in acid concentration. The order was found to be less than unity with respect to it. (figure-2)

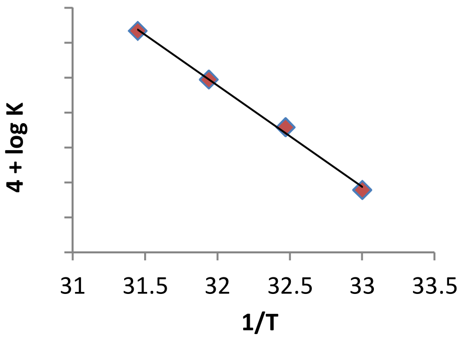
Effect of temperature on the rate of reaction

The value of k were evaluated at different temperatures and found to vary at different temperatures. Plot of log k versus 1/T was found to be linear, and the values of activation parameters with reference to catalyst were computed and results are summarized in (table 2), (figure 3).

Table 2. Effect of temperature on the rate of reaction

Temperature(K)	k x 10^{-4} (1/s)
303	2.76
308	4.20
313	6.12
318	9.50

Figure -3



Activation parameters

Parameters	value
Ea (kj mol^{-1})	45.0
ΔS* (J K^{-1} mol^{-1})	-66.95
ΔG* (kJ K^{-1} mol^{-1})	65.95
log A	13.2

Reaction Kinetics and Rate Law-

CAT being N-haloamine gives several oxidizing species in aqueous solution [20]. The concentration of each species depends upon the concentration of CAT, the nature and pH of the medium. The oxidant can exist in protonated form in an aqueous acidic solution.

CAT ionizes in aqueous acidic medium as –

$$\mathrm{CAT} + \mathrm{H}^+ \underset{k_1}{\overset{K_1}{\rightleftharpoons}} \mathrm{CATH}^+ \quad \ldots\ldots\ldots\ldots\text{(i)} \quad \text{fast}$$

$$\mathrm{CATH}^+ + \mathrm{Ru\ (III)} \rightleftharpoons [\ \mathrm{Complex}] \quad \ldots\ldots\ldots\ldots\text{(ii)} \quad \text{slow and rds}$$

$$[\mathrm{Complex}] + \mathrm{CP} \rightleftharpoons \mathrm{Products} \quad \ldots\ldots\ldots\ldots\text{(iii)} \quad \text{fast}$$

from the slow step the rate law can be written as-

$$-d\frac{[\mathrm{CAT}]\mathrm{T}}{dt} = k1\ [\mathrm{CATH}+]\ [\mathrm{Ru\ (III)}] \quad \ldots\ldots\ldots\ldots\text{(iv)}$$

The total effective concentration of CAT can be written as –

$$[\mathrm{CAT}]_T = [\mathrm{CAT}] + [\mathrm{CATH}^+] \quad \text{--------------(v)}$$

From equation (i)

$$[CAT] = \frac{[CATH^+]}{K1\,[H^+]}$$

By substituting for [CAT] in equation (v)

$$[CAT]_T = \frac{[CATH^+]}{K1\,[H^+]} + [CATH^+]$$

$$[CAT]_T = \frac{K1[CAT]T\,[H^+]}{1+K1\,[H^+]} \qquad \text{-----------------(vi)}$$

By substituting for $[CATH^+]$ from (v)

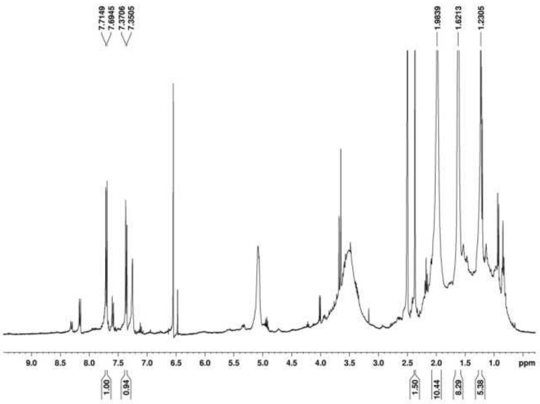
$$\text{Rate} = -d\frac{[\,CAT]}{dt} = \frac{K_1\,k1[CAT]_T\,[Ru]III\;\,[H+]}{1+K1\,[H^+]}$$

Reaction isotopic studies in heavy water indicated the increase in rate of reaction. Since D_3O^+ is definitely a stronger acid than H_3O^+ [21] and hence, this observation supports proposed mechanism.

CONCLUSION

The reaction between CAT- CP has been carried out $HClO_4$ medium. The reaction stoichiometry of 1:2 (CP : CAT) involving the oxidation of CP by CAT has been observed. The proposed mechanism is supported by the derived reaction orders, moderate values of activation energy and other thermodynamic parameters. The fairly high positive value of energy of activation indicates that the transition state is highly solvated. The overall sequence described here is consistent with all the experimental results.

Supporting information-



H^1 NMR Spectra of the product in the extracted reaction mixture

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