Full Length Research Article

INVESTIGATION OF MOLECULAR DYNAMICS FOR THE OXIDATION OF CHLORAMPHENICOL BY CAS IN HOAC-H₂O 40% (V/V) MEDIUM

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ABSTRACT

Chloramphenicol is a powerful antibiotic and is mostly used for curing both gram –negative and gram positive diseases. Ceric ammonium sulphate (CAS), a versatile oxidizing agent has been employed in acetic acid – water 40% (v/v) medium to oxidize the alcoholic groups present in chloramphenicol. This investigation has been carried out to evaluate the kinetic parameters such as rate with respect to each reactant and rate constant and thermodynamic parameters like Energy of activation(E_a), Enthalpy of activation($\Delta H^{\#}$) and Entropy of activation($\Delta S^{\#}$). With a help of these parameters the change in microbial activity of Chloramphenicol with respect to oxidation of alcoholic groups has been followed. A plausible mechanism has been suggested.

INTRODUCTION

Chloramphenicol, otherwise commercially known as Chloromycetin is a powerful antibiotic and is mostly used for curing diseases caused by both gram (-) and gram (+) bacteria (Ehrlich *et al.,* 1947). Some traditional topics in drug chemistry such as the oxidation or reduction of certain vital functional groups of drugs have continued to attract the attention of several research groups because investigation on the structural modifications and its influence on the activity of the drugs have always revealed new interesting factors. Also the most noticeable trend in current years is to evaluate the kinetic and thermodynamic parameters of the bio active molecules (Gurdeep and Chatwal, 1990). The nitro group in chloramphenicol was shown to be responsible for the antibacterial activity. For instance it has been proved that chloramphenicol loses its antibacterial activity when the nitro group is replaced by a group like –CN,-CONH₂.-NH₂,-OH,-N (CH₃)₂,-Br,-Cl,-F or –C₆H₅. In general the antibacterial activity is determined by various factors like electro negativity, molecular volume and ability to form quinanoid structure. When the benzene ring in chloramphenicol is replaced by another ring like naphthyl or cyclohexyl ring, the antibacterial

activity was shown to be greatly reduced (Alfred Burger, 1970). Also it has been proved that the alcoholic group is also a must for microbial activity since its replacement or deletion leads to the decrease of activity. Ce(IV) salts are considered to be convenient oxidizing agents for the oxidation of a large number of carbon compounds like carboxylic acids, alcohols, phenols both aliphatic and aromatic aldehyde as well ketones and heterocyclic compounds. Commonly Ce(IV)sulphates, cerium(IV) perclorates, ceric ammonium nitrate and ceric ammonium sulphate are used for the study of kinetics and mechanism of several organic compounds in general and alcohols in particular. Ce (IV) is used as oxidant not only in analysis but also in organic chemistry where it is commonly used is acetic acid (Vogel, 1986) . The solutions oxidize aldehydes and ketones at the α-carbon atom. Benzaldehyde, for example, gives benzoin while ammonium hexanitrocerate will oxidize toluene to aldehydes. The oxidation reactions appear to proceed by the initial formation of 1:1 complexes. The complexes of alcohols are known. Ce (IV) salt solutions are fairly stable. For instance even if Ce (IV) sulphate in sulphuric acid medium is subjected to boiling, there will be no decomposition. It has been revealed that there is no photochemical reaction between cerium (IV) salt solution and the solution of a reducing agent. Ce (IV) salt solution is colored where as cerium (III) is colorless and hence the kinetics of oxidation reaction can be followed by spectra photometric method (Weisberg, 1965). However if

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spectrophotometer is not available, the kinetics and mechanism of oxidation reactions by ceric ammonium sulphate can be followed either by iodometry or by titration against standard ferrous ammonium sulphate solution using ferroin as the indicator. Solutions of Ce (IV) salts are found to be highly stable in acid medium. Using Ce (IV) salt solutions, the reducing agents can be estimated very accurately even if perchloric acid is present in fairly high concentration. The oxidation of alcohols by cerium (IV) has received considerable attention recently. An intermediate complex has been shown to be formed with cerium (IV) per chlorate and ceric ammonium nitrate. But with ceric sulphate formation of such an intermediate complex has not been detected (Richardson, 1985). Literature survey has also revealed contradiction results with respect to the effect of hydrogen ion concentration on the rate of oxidation by cerium (IV) salts. With a view to studying the kinetics and mechanism of oxidation of chloramphenicol which contains two alcoholic groups using cerium sulphate as oxidant, this investigation has been taken up (Richardson, 1965).

MATERIALS AND METHODS

Reagents

All chemicals used in the experiments were of the purest available Analar grade. They were used as such without further purification unless otherwise specified.

Preparation of chloramphenicol from Chloromycetin capsules

Known weight of the contents (250 mg) of the Chloromycetin capsules (PARAXIN) was dissolved in water (100 ml). The above solution was shaken well and then extracted with petroleum ether (25ml) for four times. The petroleum ether fraction was discarded and the aqueous fraction was extracted four times with ether (50 ml). After discarding the aqueous layer, the ethereal layer was evaporated after drying. The resultant crude sample was recrystallized twice with distilled water. After recrystallisation the chloramphenicol was obtained as a white, needle-like crystals or elongated plates. The melting point (149.8 - 150.3°C) was noted which is found to being good agreement with the reported value (149.0 – 150.2°C).

Experimental methods

A mixture of chloramphenicol solution in glacial acetic acid (4 ml), glacial acetic acid (12 ml) perchloric acid (4 ml) and double distilled water (16 ml) was taken in stoppered conical flask and kept in thermostat at 308 K. In another stoppered conical flask ceric ammonium sulphate (50 ml) solution was taken and kept in the same thermostat. After about half an hour, the oxidant (4ml) was added to the reaction mixture and shaken well. Immediately a known volume of the reaction mixture (2ml) was pipetted out into a clean conical flask containing ferrous ammonium sulphate solution (2 ml) so as to arrest the oxidation reaction. A piece of ice was also added. To this solution, one drop of ferroin indicator was added and titrated against ceric ammonium sulphate taken in the burette. The end point is the just appearance of pale blue color. The above procedure was repeated for known intervals of time. The infinite reading was taken by heating the reaction mixture

at 50°C for about an hour in a water bath. A graph was drawn by plotting $\log (V^\infty - Vt)$ versus time. A straight line was obtained. The slope of the line was determined and the pseudo – first order rate constant was calculated. The above experiments were repeated with the same substance and the same oxidant and the results were calculated. It was of our interest to carry out experiments to study the effect of changing the concentration of ceric ammonium sulphate and that of chloramphenicol on the rate constant. It was also planned to evaluate thermodynamic parameters. One mole of chloramphenicol and 6 moles of ceric ammonium sulphate were kept under kinetic condition for 72 hours. At the end of the completion of the reaction, the excess /unreacted ceric ammonium sulphate was estimated by pipetting out 2 ml of the reaction mixture into a conical flask containing exactly 2 ml of ferrous ammonium sulphate solution. The excess ferrous ammonium sulphate solution was titrated against standard ceric ammonium sulphate. The stoichiometry was found to be 1:4. The reaction mixture containing chloramphenicol and ceric ammonium sulphate in the molar ratio 10:1 was kept under kinetic condition for 48 hours. The portion of the solution was diluted with sodium acetate solution (4%) and then treated with 2, 4-dinitrophenyl hydrazine solution. After cooling for 24 hours, the separated yellow precipitate was filtered, washed with distilled water and dried. The melting point was determined and it was found to be 180.9°C. The reaction mixture was extracted with ether and the ethereal layer was then extracted with sodium bicarbonate solution. The aqueous layer was then extracted with ether. The ether layer was evaporated. The residue obtained, on qualitative analysis and spectral analysis (UV-VIS, FT- IR, ^{1}H- NMR and ^{13}C-NMR) show the presence of carboxylic acid group.

RESULTS AND DISCUSSION

The experimental results on the study of the effect of variation of concentration of ceric ammonium sulphate on the oxidation of chloramphenicol are given in representative Table 1 and respective kinetic plots of $\log (V^\infty - Vt)$ versus time were drawn and are shown in Figure 1. The titre values of the study of effect of variation of concentration of chloramphenicol are given in representative Table - 2. Respective kinetic plots are shown in Figure 2. The data for the study of effect of variation of concentration of perchloric acid on rate constant was given in representative table-3 and the respective kinetic plots are shown in Figure 3. The data for the study of effect of variation of temperature on rate constant at different pH is given in table representative table-4 and the relevant kinetic plots are shown in Figure 4. The data for the study of effect of variation of chloramphenicol on rate constant was given in table representative table-5 and the plot of $\log k'_{obs}$ versus $\log$ [CMPL] was drawn and is shown in Figure-5. The plot 1/ [CMPL] versus $1/k'obs$ is shown in Figure 6. Table 6 represents the effect of variation of temperature on rate constant and Figure7 represents Arrhenius plots. The data for the effect of variation of ceric ammonium sulphate on rate constant was given in representative Table-7. The data for the effect of variation of perchloric acid on rate constant was given in representative table-8. The thermodynamic parameters are given in representative table-9. The relationship between $\Delta H^\#$ and $\Delta S^\#$ was shown in Figure 8.

Table 1. Effect of variation of concentration of ceric ammonium sulphate

[CMPL] = 1.0 X 10^{-2} M HOAc-H_2O = 40 % (v/v)
[CAS] = 1.0 X 10^{-4} M
Temp. = 308 K
[$HClO_4$] = 5.0 X 10^{-3} M

Time, min	VCAS = V_t,ml	$(V\infty - Vt)$ ml	$10+\log(V\infty - Vt)$
0	18.00	3.8	10.5798
10	18.20	3.6	10.5563
20	18.40	3.4	10.5314
30	18.55	3.25	10.5118
40	18.70	3.1	10.4913
50	18.90	2.9	10.4623
60	19.05	2.75	10.44
70	19.30	2.5	10.3979
80	19.40	2.4	10.3802
90	19.60	2.2	10.3424
∞	21.80	-	-

Table 2. Effect of variation of concentration of chloramphenicol

[CMPL] = 1.0 X 10^{-3}M   HOAc-H_2O = 40 % (v/v)
[CAS] = 1.0 X 10^{-3} M
Temp. = 308 K
[$HClO_4$] = 5.0 X 10^{-3} M

Time, min	$V_{CAS} = V_t$,ml	$(V\infty - Vt)$ ml	$10+\log(V\infty - Vt)$
0	21.30	3.25	10.5118
10	21.45	3.10	10.4913
20	21.60	2.95	10.4698
30	21.75	2.80	10.4471
40	21.85	2.70	10.4313
50	22.00	2.55	10.4065
60	22.15	2.40	10.3802
70	22.25	2.30	10.3617
80	22.35	2.20	10.3424
90	22.55	2.00	10.3010
∞	24.55	-	-

Table 3. Effect of variation of concentration of perchloric acid

[CMPL] = 1.0 X 10^{-2} M   HOAc-H_2O = 40 % (v/v)
[CAS] = 1.0 X 10^{-3} M
Temp. = 308 K
[$HClO_4$] = 0.5 X 10^{-3} M

Time, min	$V_{CAS} = V_t$,ml	$(V\infty - Vt)$ ml	$10+\log(V\infty - Vt)$
0	21.40	3.05	10.4842
10	21.55	2.90	10.4623
20	21.75	2.70	10.4313
30	21.90	2.55	10.4065
40	22.05	2.40	10.3802
50	22.25	2.20	10.3424
60	22.35	2.10	10.3222
70	22.45	2.00	10.3010
80	22.55	1.90	10.2787
90	22.65	1.80	10.2552
∞	24.45	-	-

Table 3 Effect of variation of concentration of perchloric acid

[CMPL] = 1.0 X 10^{-2} M HOAc-H_2O = 40 % (v/v)
[CAS] = 1.0 X 10^{-3} M
Temp. = 308 K
[$HClO_4$] = 0.75 X 10^{-3} M

Time, min	$V_{CAS} = V_t$,ml	$(V\infty - Vt)$ ml	$10+\log(V\infty - Vt)$
0	22.40	2.20	10.3424
10	22.60	2.00	10.3010
20	22.70	1.90	10.2787
30	22.80	1.80	10.2552
40	23.00	1.50	10.1760
50	23.10	1.50	10.1760
60	23.25	1.35	10.1303
70	23.40	1.20	10.0800
80	23.45	1.15	10.0606
90	23.55	1.05	10.0211
∞	24.60	-	-

Table 4 Effect of variation of temperature on rate constant at pH= 1.80

[CMPL] = 1.0 X 10^{-2} M   HOAc-H_2O = 40 % (v/v)
[CAS] = 1.0 X 10^{-3} M
Temp. = 308 K
[$HClO_4$] = 0.5 X 10^{-3} M

Time, min	$V_{CAS} = V_t$,ml	$(V\infty - Vt)$ ml	$10+\log(V\infty - Vt)$
0	21.40	3.05	10.4842
10	21.55	2.90	10.4623
20	21.75	2.70	10.4313
30	21.90	2.55	10.4065
40	22.05	2.40	10.3802
50	22.25	2.20	10.3524
60	22.35	2.10	10.3222
70	23.45	2.00	10.3010
80	23.55	1.90	10.2787
90	23.45	1.80	10.2552
∞	24.45	-	-

Table 5. Effect of ceric ammonium sulphate on rate constant

[CMPL] = 1.0 X 10^{-3} M HOAc-H_2O = 40 % (v/v)
[$HClO_4$] = 5.0 X 10^{-3} M Temp. = 308K

[CAS] X 10^4,M	K' x 10^5,sec^{-1}
1.0	9.2356
1.5	10.4311
2.0	11.7231
2.5	13.4968
3.0	14.8618

Table 6. Effect of chloramphenicol on rate constant

[CMPL] = 1.0 X 10^{-3} M HOAc-H_2O = 40 % (v/v)
[$HClO_4$] = 5.0 X 10^{-3} M Temp. = 308K

[CMPL] X 10^3,M	K'x10^5,sec^{-1}	$10 + \log k'_{obs}$	$10+\log[CMPL]$
1.0	8.1038	5.9087	7.0000
1.5	6.5905	5.8189	7.1761
2.0	4.3333	6.6368	7.3010
2.5	4.0240	5.6047	7.4000
3.0	3.9022	5.5913	7.4771

Table 7. Effect of variation of 1/ [CMPL] on 1/k'$_{obs}$

K'x10^5,sec^{-1}	[CMPL] X 10^3,M	$1/k'_{obs}$	$1/[CMPL]$
8.1038	1.0	12339.89	1000.00
6.5905	1.5	15173.36	666.66
4.3333	2.0	23077.10	500.00
4.0240	2.5	24850.89	400.00
3.9022	3.0	25626.57	333.33

Table 8. Effect of variation of [$HClO_4$] on rate constant

[CMPL] = 1.0 X 10^{-2} M
HOAc-H_2O = 40 % (v/v)
[CAS] = 1.0 X 10^{-3} M Temp. = 308K

[CAS] X 10^4,M	K' x 10^5,sec^{-1}
0.5	8.5616
0.75	12.3666
1.0	13.9133
1.5	14.5233
2.0	16.0783

Table 9 Effect of variation of Temperature on rate constant at pH= 1.80

Temp., K	K' x 10^5,sec^{-1}	$(1/T) X10^3$	$10+\log_e k'$
308	8.5616	3.246	0.634
313	13.2596	3.195	1.071
318	15.0790	3.145	1.200

Table 10 Thermodynamic parameters for the oxidation of chloramphenicol   by CAS at pH= 1.80

Temp., K	K' x 10^5 ,sec^{-1}	$\Delta H^{\#}$, cals mol^{-1}	$\Delta S^{\#}$, eu
308	8.5616	3660.05	-65.2851
313	13.2596	3650.11	-64.6695
318	15.0790	3640.18	-64.6601
	Mean	3650.11	-64.5115

**Table 11 Thermodynamic parameters for the oxidation of chloramphenicol by CAS at different   pH**

pH	$\Delta H^{\#}$, cals mol^{-1}	$\Delta S^{\#}$, eu
1.80	3650.11	-64.57
1.90	4977.63	-60.28
2.00	2557.26	-67.76
2.10	1992.36	-69.39
2.20	4345.56	-61.80
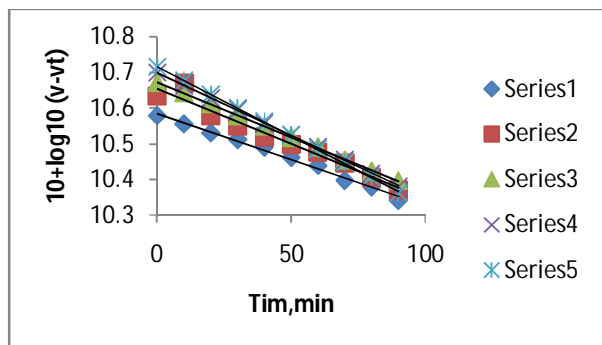
Fig.1: Effect of change of concentration of CAS on the oxidation of chloramphenicol at 308°K

[CAS]=1.0×10^{-4}M (seies-1); 1.5×10^{-4}M (seies-2); 2.0×10^{-4}M (seies-3); 2.5×10^{-4}M (seies-4); 3.0×10^{-4}M (seies-5)
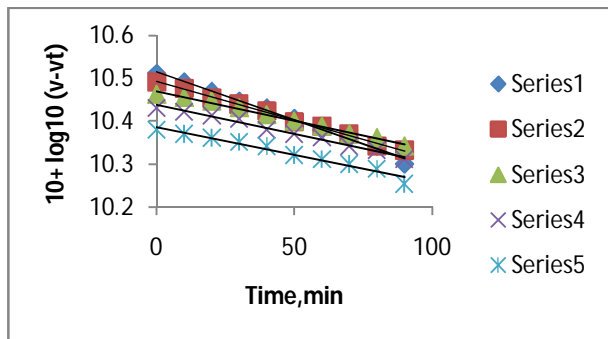


Fig.2: Effect of change of concentration of Chloramphenicol on the oxidation of   chloramphenicol at 308°K

[CMPL]=1.0×10^{-3}M (seies-1); 1.5×10^{-3}M (seies-2); 2.0×10^{-3}M (seies-3); 2.5×10^{-3}M (seies-4); 3.0×10^{-3}M (seies-5)
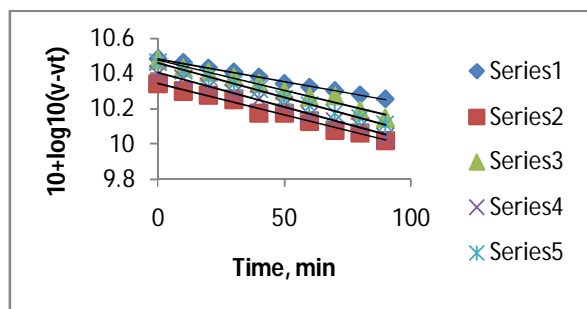

Fig.3: Effect of change of concentration of Perchloric acid on the oxidation of chloramphenicol at 308°K

[HClO$_4$]=0.5×10^{-3}M (seies-1); 0.75×10^{-3}M (seies-2); 1.0×10^{-3}M (seies-3); 1.5×10^{-3}M (seies-4); 2.0×10^{-3}M (seies-5)
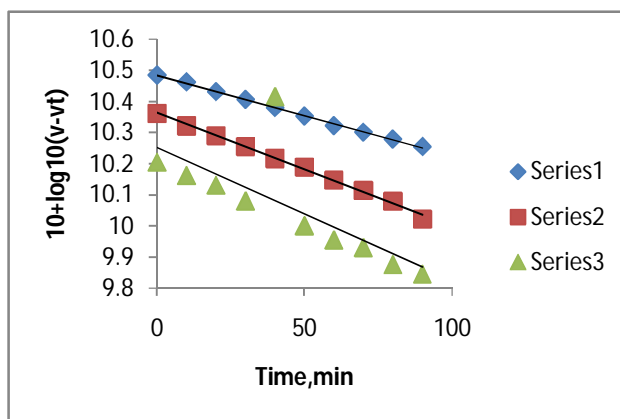
Fig. 4.Effect of variation of temperature on rate constant at pH = 1.80 Temperature =308 K (series-1); 318 (series-2); (series-3) (Representative plot)
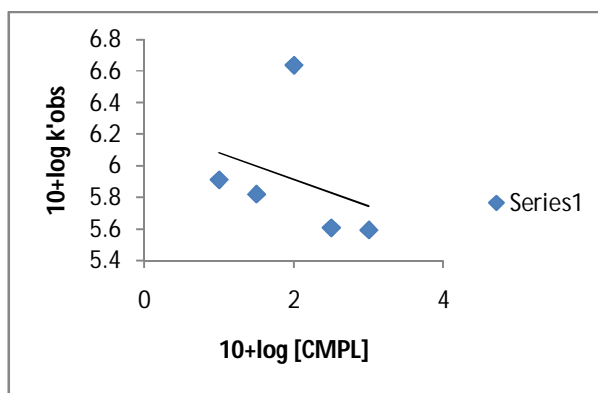
Fig.5. Effect of variation of chloramphenicol on rate constant
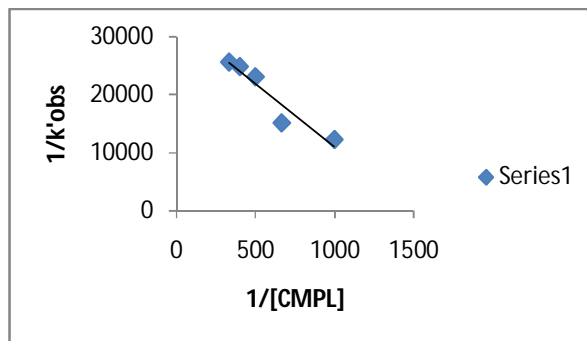
Fig.6. Effect of variation of 1/chloramphenicol on 1/rate constant

The data of the kinetics of oxidation of chloramphenicol by ceric ammonium sulphate reveals the fact that the reaction follows first order kinetics with respect to ceric ammonium sulphate and a fractional order with respect to chloramphenicol. In the experimental part, concentration of chloramphenicol was always kept greater than that of ceric ammonium sulphate. When [chloramphenicol] = 1.0 x 10^{-2} M; [HClO$_4$] =5.0 x 10^{-3} M; acetic acid – water = 40 % (v/v); temperature = 308 K and if the [ceric ammonium sulphate] x 10^4 is 1.0, 1.5, 2.0, 2.5 and 3.0, the (pseudo-first order rate constant) x 10^5 was found to be 9.2356, 10.4311, 11.7231,
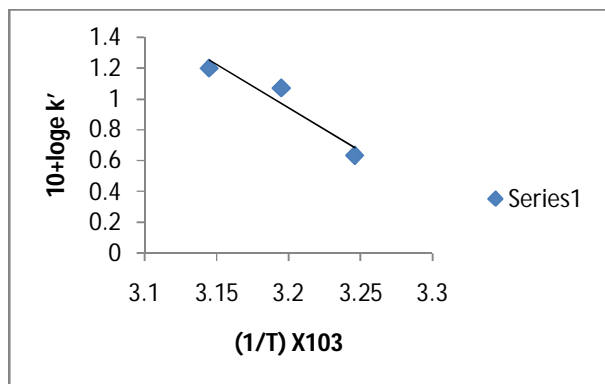
Fig.7. Effect of variation of temperature on rate constant at pH = 1.80 (Representative plot)
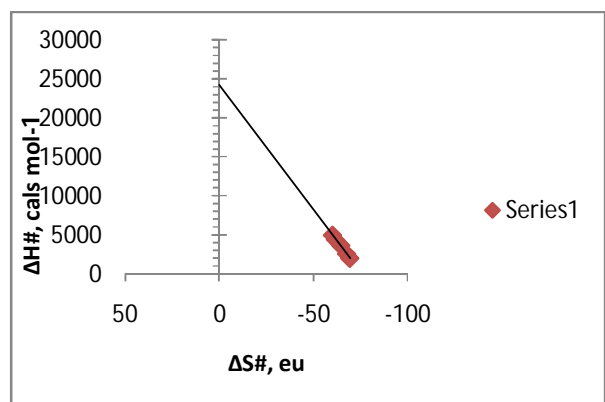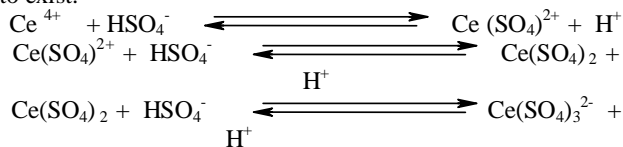

Fig.8. Relationship between $\Delta H^{\#}$ and $\Delta S^{\#}$

13.4968 and 14.8618 respectively. The plot of log (V∞Vt) versus time was found to be linear. Hence it was concluded that the reaction follows first order kinetics. The effect of change of concentration of chloramphenicol on rate constant was also determined. When [ceric ammonium sulphate] = 1.0 x 10^{-3} M; $[HClO_4]$ = 5.0 x 10^{-3} M; acetic acid – water = 40 % (v/v); temperature = 308 K and if the [chloramphenicol] x 10^2 is 1.0, 1.5, 2.0, 2.5 and 3.0, the (pseudo-first order rate constant) x 10^5 was found to be 8.1038, 6.5909, 4.3333, 4.0240 and 3.9022 sec $^{-1}$. These results indicate that the reaction follows fractional order kinetics with respect to concentration of chloramphenicol. Literature survey has also revealed that oxidation of 1-phenyl-propan-1-ol, benzhydrol; 1-naphthylmethyl carbinol by cerium (IV) per chlorate in aqueous acetic acid medium confirms a general mechanism of the rapid formation of 1:1 complex followed by a slow decomposition of the complex. In a mixture of cerium (IV) salt and sulphuric acid, the following equilibriums were shown to exist.

$$Ce^{4+} + HSO_4^- \rightleftharpoons Ce(SO_4)^{2+} + H^+$$
$$Ce(SO_4)^{2+} + HSO_4^- \rightleftharpoons Ce(SO_4)_2 + H^+$$
$$Ce(SO_4)_2 + HSO_4^- \rightleftharpoons Ce(SO_4)_3^{2-} + H^+$$

Where the values of K_{eq1}, K_{eq2} and K_{eq3} are given as 3500, 200 and 20 respectively. These values suggest that ceric sulphate exists mainly as $Ce(SO_4)_3^{2-}$ ions in fairly strong acidic solutions. The formation of coordination complex in a

reaction between $Ce(SO_4)_3^{2-}$ and the ligand (L) is expected only if K_{eq4} is greater than K_{eq3}.

$$Ce(SO_4)_3^{2-} + L \rightleftharpoons Ce(SO_4)_2 L + SO_4^{2-}$$
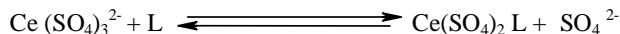
However the value of K_{eq4} for several Ce^{4+} - substrate complex, is found to be much less than 20. A graph was drawn by plotting 1/pseudo – first order rate constant versus 1/ [chloramphenicol]. A straight line, not passing through the origin, with a definite intercept, was obtained. Such a curve indicates the formation of 1:1 complex in the mechanism of oxidation of chloramphenicol. According to Duke, many homogeneous oxidation reduction reactions involve the formation of oxidant-substrate co-ordination complexes and later this was substantiated by many co-workers. A review on ceric ion oxidation of organic compound is available. Product analysis shows that the kinetic reaction mixture, at the end of reaction, forms a dinitrophenyl hydrazine derivative with 2, 4-dinitro phenyl hydrazine, indicating the presence of a carbonyl function in the product. The kinetic reaction mixture at the end of the reaction was then extracted with ether repeatedly. The ethereal layer was extracted with sodium bicarbonate solution. After neutralization the solution was extracted with ether. After drying with anhydrous sodium sulphate it was evaporated. The residue shows positive answer for carboxylic acid group. Based on the data available at present, we would like to suggest the following probable mechanism for the oxidation of chloramphenicol by ceric ammonium sulphate. Since the reaction follows only fractional order kinetics with respect to chloramphenicol and the plot of 1/pseudo-first of rate constant versus 1/ [chloramphenicol] gives a linear curve with a definite intercept, formation of a 1:1 complex between the oxidant and substrate is expected. Formation of such a complex is again confirmed by the fact of the development of deep yellow color during the mixing of chloramphenicol with ceric ammonium sulphate. This complex may decompose and give a free radical which may react with another cerium (IV) ion to give the carbonyl compound. So the following probable mechanism is proposed;

The above mechanism is in good agreement with the result of stoichiometry determination. It has already been reported in the literature for the oxidation of chloramphenicol by ceric ammonium sulphate in acetic acid – water 70% (V/V) medium that change of ionic strength of the medium does not reflect any appreciable change on the rate constant. Hence, it is inferred that the rate-determining step does not involve either oppositely charged ions of the same charge as the reactant species. If the above proposed mechanism is assumed to be correct, the rate of the reaction should decrease with the increase of concentration of hydrogen ion, because the rate determining step involves release of hydrogen ions. However the results of the present investigation contradict with the above inference. Experimentally it has been proved that the rate increases with the increase of concentration of hydrogen ions. For instance, if $HClO_4$ x 10^3 is 0.5, 0.75, 1.0 1.5 and 2.0, the pseudo-first order rate constant x 10^5 is 8.5616, 12.3666, 13.9133, 14.5233 and 16.0783 sec^{-1} respectively. Therefore there may be a possibility of existence of a pre-equilibrium step between chloramphenicol and hydrogen ion to form protonated species which may be the reacting species rather than chloramphenicol itself. Experiments were carried out to obtain Arrhenius plots at different temperature for different pH

value. From Arrhenius plots at different temperatures, thermodynamic parameters such as E_a, $\Delta H^\#$ and $\Delta S^\#$ were calculated. The thermodynamic parameters were found to vary with the variation of pH. Such variation is expected if a pre-equilibrium step is expected. A graph was drawn $\Delta H^\#$ versus $\Delta S^\#$. A straight line was obtained which is in accordance with the above inference. The above proposed mechanism can be improved by carrying out further experiments as suggested below. Free radical formation can be confirmed by electron sin resonance (E.S.R) spectroscopy or by reaction with acryl nitrile. The exact nature of the product may be confirmed by carrying out spectral studies. Formation of oxidant-substrate complex may be confirmed by Arden's method. These experiments may through light on the exact mechanism of oxidation of chloramphenicol by ceric ammonium sulphate.

Conclusion

The kinetics of oxidation of chloramphenicol by ceric ammonium sulphate has been studied in 40% acetic acid – aqueous medium. The reaction rate was found to be first order with respect to the concentration of ceric ammonium sulphate and fractional order with respect to the concentration of chloramphenicol. The rate of the reaction is increased with the increase in concentration of perchloric acid. The rate of the reaction has been studied at three different temperatures. The energy of activation (E_a), enthalpy of activation ($\Delta H^\#$) and entropy of activation ($\Delta S^\#$) were calculated. An appropriate mechanism has also been suggested.

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