WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 6, 1729-1738. Research Article ISSN 2277– 7105

Ru(III) CATALYZED OXIDATION OF PARACETAMOL BY CHLORAMINE-T IN AQUEOUS ALKALINE MEDIUM- A KINETIC AND MECHANISTIC STUDY

Amrita Srivastava* and Neha Agarwal

Department of Chemistry, University of Lucknow, Lucknow, U. P., India.

Article Received on
04 April 2015,

Revised on 24 April 2015,
Accepted on 20 May 2015

***Correspondence for Author**
Amrita Srivastava
Department of Chemistry,
University of Lucknow,
Lucknow, U. P., India.

ABSTRACT

The oxidation kinetics of paracetamol by chloramine-T in NaOH medium has been studied at 313K. The reaction had shown first order dependence on CAT and Ru(III). First order dependence on Paracetamol at its low concentrations but tending towards zero order at its higher concentrations. The reaction showed negative fractional order w.r.t $[OH^-]$. The rate of reaction decreased with decreasing dielectric constant of the medium which was done by adding CH_3COOH**.** Variation of chloride ion, mercuric acetate and ionic strength did not bring any significant change on the rate. The oxidation product had been identified by FTIR spectroscopic techniques. Thermodynamic parameters were computed by performing the kinetic runs at various temperatures. A mechanism consistent with observed parameters is proposed and rate law is derived.

KEYWORDS: *Paracetamol, Ru(III)Chloride, Chloramine-T, Kinetics, Oxidation.*

1. INTRODUCTION

In recent times a great attention has been paid to assay the compounds which are of biological, medicinal and pharmaceutical importance. Paracetamol (4-hydroxyacetanilide or acetaminophen) is a versatile analgesic and antipyretic medicine which finds extensive applications pharmaceutically. This drug is an effective analgesic and has very few side effects when used in the prescribed dose. Ingestion of an overdose is potentially fatal and may lead to liver failure, severe hepatotoxicity and nephrotoxicity.[1-3] It is also used as an intermediate in pharmaceutics (as precursor of Penicillin), photographic chemical, H_2O_2 stabiliser and azo dye.[4-6] The development of a simple, economical and accurate analytical method for the determination of active ingredients of paracetamol would be useful for many commercial applications and also in investigating the stability of paracetamol in pharmaceutical preparations for quality control.[7,8]

Aromatic N-halosulfonamides act as mild oxidants in both acid and alkaline solutions due to the presence of strongly polarized N-linked halogen in +1 state. Many organic substrates were oxidized by these sulfonamides and the kinetic and mechanistic aspects of these reactions are well documented.[9-11] A prominent member of this group Chloramine-T (CAT) is used as haloginating and oxidizing agent in acidic and basic media.[12-16] It is a versatile oxidizing agent and has shown a variety of kinetic results due to formation of various oxidizing species depending upon pH of the medium.

Recently, use of transition metals as catalyst in various redox processes has attracted considerable interest.[17] Ru (III) Chloride is known as a nontoxic and homogenous catalyst[18] but a little attention is paid to explore role of Ru(III) as catalyst in alkaline media. In the present communication we are reporting kinetic, mechanistic and thermodynamic aspects of oxidation of acetaminophen by chloramine-T in alkaline medium at 313 K.

2. EXPERIMENTAL

2.1 MATERIALS AND METHODS

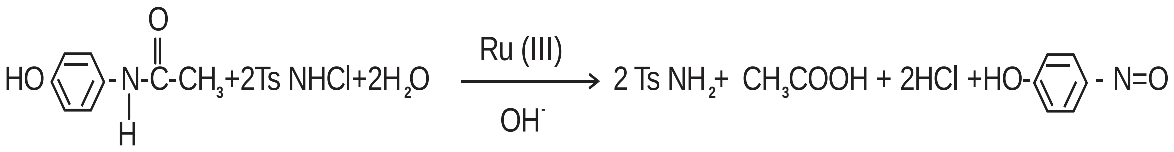
All the chemicals were A.R. grade and double distilled water was used throughout the investigations. A solution of paracetamol (CDH Ltd, New Delhi) of required strength was freshly prepared every time. The Stock solution of CAT (Chloramine-T) was prepared in double distilled water and its concentration was checked iodometrically. The stock solution of Ruthenium Chloride was prepared by dissolving the known amount in HCl of known strength in a black coated flask to avoid photochemical effects. KCl, NaOH, $Hg(OAc)_2$ of known strength are also used without further purification. All other reaction vessels were also coated black from outside to avoid any photochemical degradation.

A thermostatic water bath was used to maintain the desired temperature. Aliquots of the reaction mixture were placed in the thermostat-controlled water bath, which was per-equilibrated at 313 K. Requisite volume of paracetamol solution, also thermo stated at the same temperature was rapidly pipette out and poured into the reaction vessel. The total volume of the reaction mixture was 50 ml each time. 5 ml aliquots of the reaction mixture was pipetted out at different intervals of time and quenched with 4% acidified KI solution.

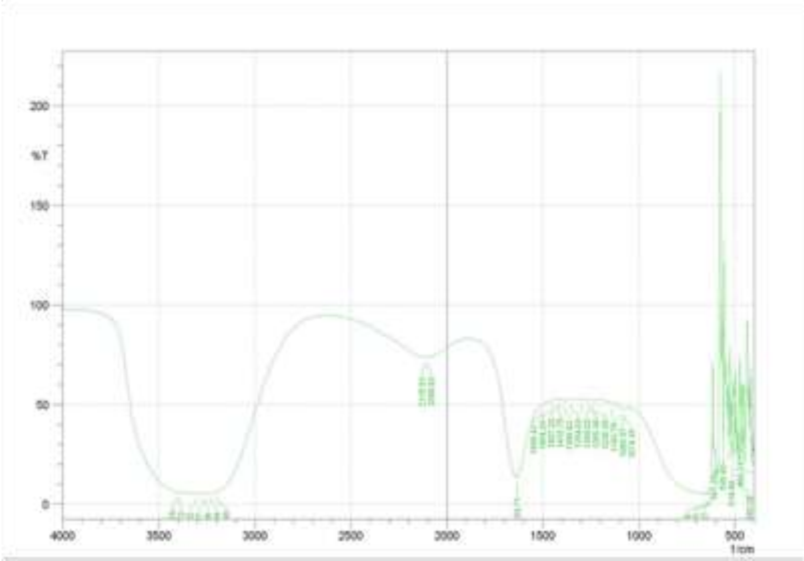
The progress of the reaction was monitored by iodometric estimation of unreacted oxidant in measured aliquots of the reaction mixture withdrawn at regular intervals of time. The kinetic runs were carried out at 313 K.

2.2 Stoichiometry and product analysis

Different sets of the reaction mixture with excess of CAT were kept for 48 hrs at room temperature. Determination of unconsumed CAT in each set confirmed 1:2 stoichiometry between paracetamol and CAT.



The reaction products were extracted with ether. From the ether layer the oxidation product was identified as quinone oxime. The nature of quinone oxime was confirmed by FTIR (1652 cm^{-1} due to C=O stretching, 1615 cm^{-1} due to C=N stretching of oxime, 3332 cm^{-1}due to OH stretching) . Acetic acid was confirmed by spot test.[19]



FTIR spectra of the reaction product extracted in ether

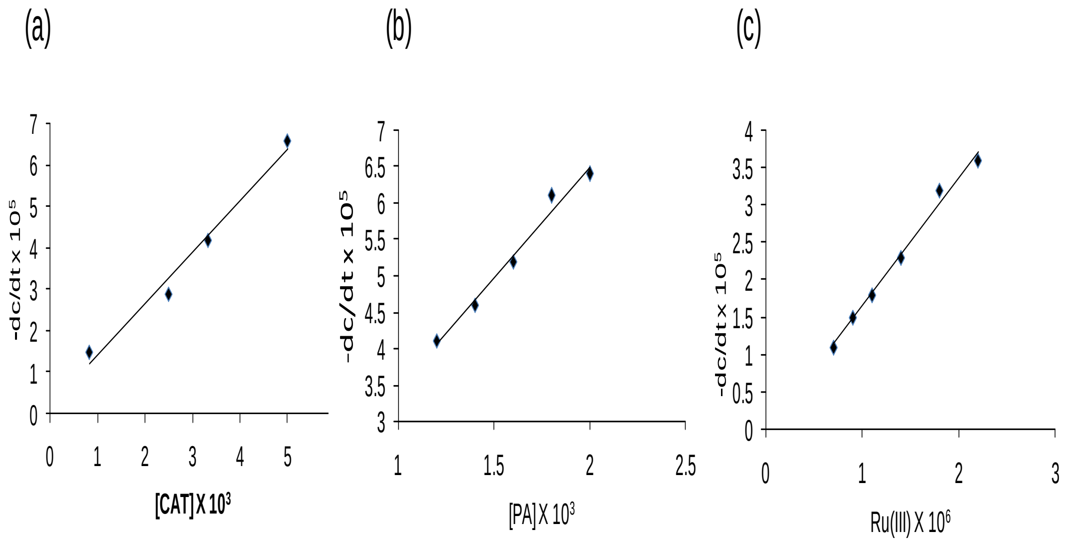
3. KINETIC RESULTS AND DISCUSSION

Effect of reactants concentration on the rate: The kinetics measurements were performed by varying the concentration of any one reactant and keeping the concentrations of all other reactants constant. The values of K_1 remain unaltered with the variation of [CAT]. The same was also confirmed by the plot of [CAT] versus (-dc/dt) was linear passing through the origin (graph-a), indicated a first order dependence of the rate of reaction on [CAT]. The constant K on varying the concentration confirmed the first-order dependence on Ru(III) also. The plot of rate of reaction (-dc/dt) versus [Ru] indicated first order with respect to catalyst. Reactions were studied under similar experimental conditions by varying the concentration of [PA]. First order dependence on paracetamol at its low concentrations and tends to zero order at its higher concentrations as seen from the (table-1).

Table-1: Effect of variation of substrate, oxidant, catalyst & medium at 313K

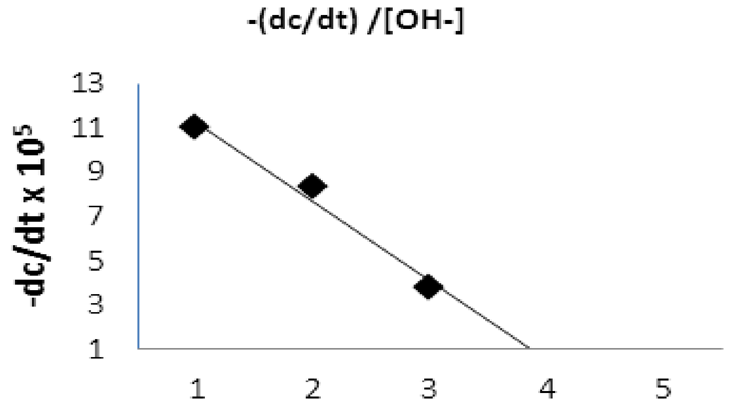
[PA] X 10^3	[CAT] X 10^3	Ru(III) X 10^6	[OH^-] X 10^3	-dc/dt x 10^5	K_1 x 10^4
1.2	1.0	2.0	1.0	4.10	.034
1.4	1.0	2.0	1.0	4.60	.033
1.6	1.0	2.0	1.0	5.20	.033
1.8	1.0	2.0	1.0	6.10	.034
2.0	1.0	2.0	1.0	6.40	.032
2.2	1.0	2.0	1.0	6.60	.030
2.5	1.0	2.0	1.0	6.70	-
5.0	1.0	2.0	1.0	6.80	-
1.0	0.83	2.0	1.0	1.50	1.3
1.0	1.25	2.0	1.0	2.70	1.4
1.0	2.50	2.0	1.0	2.90	1.3
1.0	3.33	2.0	1.0	4.20	1.4
1.0	5.0	2.0	1.0	6.60	1.4
1.0	1.0	0.7	1.0	1.10	.016
1.0	1.0	0.9	1.0	1.50	.016
1.0	1.0	1.1	1.0	1.80	.016
1.0	1.0	1.4	1.0	2.30	.016
1.0	1.0	1.8	1.0	3.20	.017
1.0	1.0	2.2	1.0	3.60	.016
1.0	1.0	2.0	0.66	13.6	.206
1.0	1.0	2.0	0.83	11.0	.312
1.0	1.0	2.0	1.25	8.30	.060
1.0	1.0	2.0	2.5	3.80	.015
1.0	1.0	2.0	3.33	0.58	.002

[$Hg(OAc)_2$] = 1.00 x 10^{-3} M, [NaOH] = 1.00 x 10^{-3} M, [KCl] = 1.00 x 10^{-3} M



Plot between (a)[CAT]× 10^{-3} (b) [PA]× 10^{-3} and (c) Ru(III) X 10^{6} M vs. [-dc/dt]× 10^{5} $ML^{-1}S^{-1}$

Effect of [OH^-] on the rate: Increase in [OH^-] by adding NaOH brought the decrease in the rate of reaction (table-1). The plot of log k versus [OH^-] shows its negative effect on the rate of reaction.



(d) Plot **between [OH^-] x 10^{-3} vs. (-dc/dt) x 10^{5} $ML^{-1}S^{-1}$** – showing negative effect of basic medium on the rate).

Effect of ionic strength on the rate: Effect of ionic strength was studied by adding NaClO4. The rate of reaction did not show any significant change confirming the involvement of non ionic species in the rate determining step.

Effect of temperature on the rate: The effect of temperature was studied by carrying out the reaction at different temperatures (303, 308, 313, 318) but keeping other experimental conditions constant (table-3). The activation parameters were computed from the Arrhenius plot of log k versus 1/T (figure-).

Effect of dielectric constant on the rate: The rate of reaction decreased by decreasing dielectric constant of the medium. This was checked by adding and varying CH_3COOH to the reaction mixture.

Table-2: Effect of variation of KCl, $NaClO_4$ and $Hg(OAc)_2$ at 313K

[KCl] x 10^3 M	$[Hg(OAc)_2]$ x 10^3 M	$[NaClO_4]$ x 10^3 M	(-dc/dt) x 10^5
1.00	1.00	-	2.22
1.40	1.00	-	2.18
2.00	1.00	-	2.22
2.41	1.00	-	2.18
1.00	1.20	-	1.50
1.00	1.66	-	1.61
1.00	2.50	-	1.51
1.00	3.33	-	1.70
1.00	1.00	1.1	.27
1.00	1.00	1.5	.26
1.00	1.00	2.0	.27

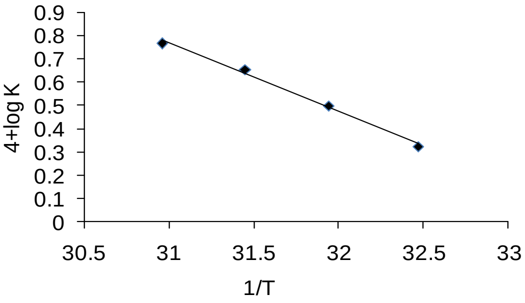
Solution conditions: [CAT]= 1 x 10^{-3} M, [PA] = 1 x 10^{-3} M, [Ru(III)] = 2 x 10^{-6} M, $[OH^-]$ = 1 x 10^{-3} M

Table-3: Effect of temperature and activation parameters on the rate

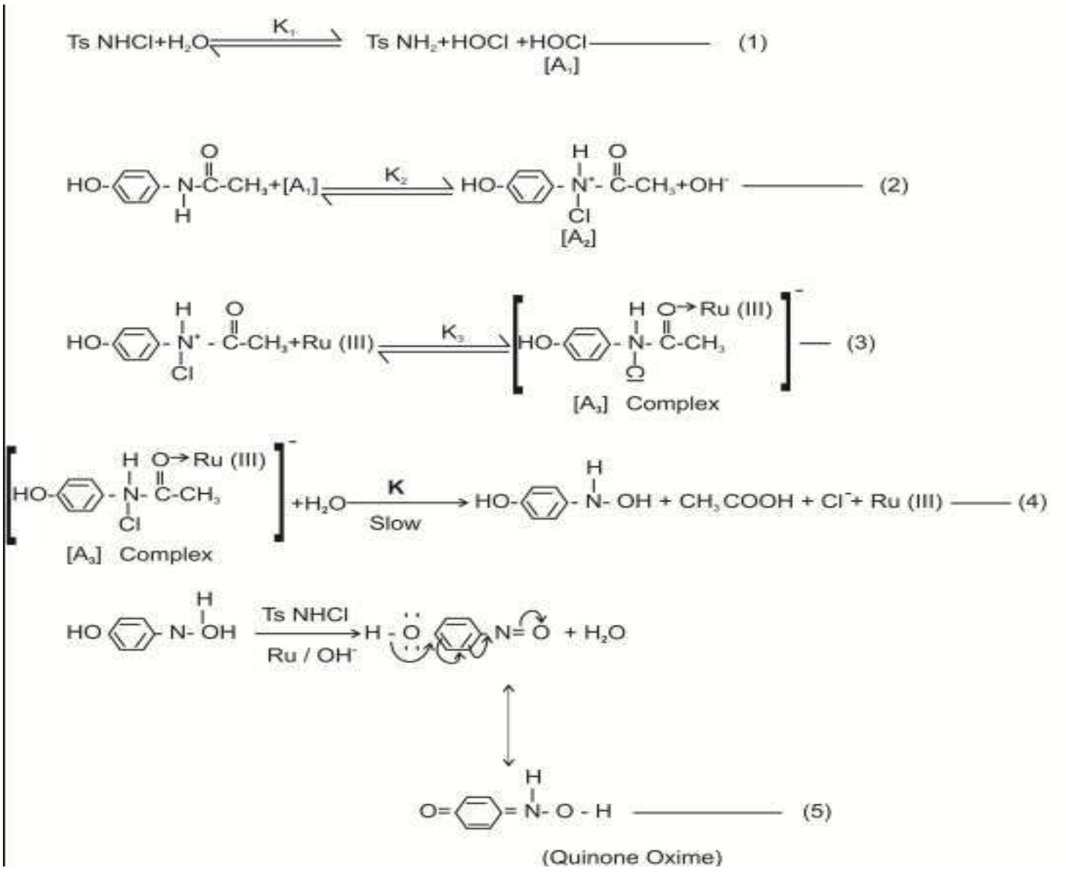
Temperature (K)	K_1 x 10^5 (S^{-1})	Activation parameter
313	2.11	-
318	3.16	-
323	4.52	-
328	5.83	-
Ea (kj mol^{-1})	-	45.9
ΔS* (J K^{-1} mol^{-1})	-	-92.87
ΔG* (kJ K^{-1} mol^{-1})	-	74.96
log A	-	8.15

Solution conditions : [CAT]= 1 x 10^{-3} M, [PA] = 1 x 10^{-3} M, [Ru(III)] = 2 x 10^{-6} M, $[OH^-]$ = 1 x 10^{-3} M, , [KCl] = 1.00 x 10^{-3} M

Plot of 1/T vs. log K



4. Reaction mechanism and rate law



On the basis of above discussion and mechanism the rate of reaction and rate law may be derived as-

Rate $= -d\,\frac{[CAT]}{dt} = 2\,K\,[\text{complex}]$

the concentration of complex (A_3) can be obtained by applying steady state approximation –

$d\,\frac{[\text{complex}]}{dt} = K_3\,[A_2]\,[\text{Ru(III)}] - K\,[A_3] - [A_3] = 0$

Therefore, $K_3\,[A_2]\,[\text{Ru(III)}] = K\,[A_3] + [A_3]$

$[A_3] = \frac{K_3\,[A_2][\text{Ru(III)}]}{[K+1]}$ --(6)

Now $[A_2]$ can be obtained as:

$-d \frac{[A2]}{dt} = K_2 [A_1] [PA] - [A_2] [OH^-]$ ---------------------------------(7)

$[A_2] = \frac{K_2 [A1][PA]}{[OH^-]}$

Now $[A_1]$ can be obtained as:

$-d \frac{[A_1]}{dt} = K_2 [CAT] - [TsNH_2] [A_1]$ -----------------------------------(8)

$[A_1] = \frac{K_1 [CAT]}{[TsNH_2]}$

On putting the values of A_2 and A_1 in equation (6)

$A_3 = \frac{K_3 [Ru] K_2 [A1][PA]}{[K+1][OH^-]}$

$A_3 = \frac{K_3 K_2 K_1 [Ru] [PA][CAT]}{[TsNH_2][OH^-]}$ (on neglecting the term [K+1])

The rate of reaction can be written as-

$\text{Rate} = \frac{2 K_3 K_2 K_1 [Ru] [PA][CAT]}{[TsNH_2][OH^-]}$ ---------------------------(9)

Now, the total concentration of [CAT] can be written as-

$[CAT]_{T} = [CAT] + [A_1] + [A_2] + [A_3]$ ------------------------------------(10)

On substituting the values of $[A_1]$, $[A_2]$,$[A_3]$ in equation (10) the following equation results-

$[CAT] = [CAT]_T [OH^-] [TsNH_2] / [OH^-] [TsNH_2] + K_1 [OH^-] + K_1 K_2 [PA] + K_1 K_2 K_3 [Ru] [PA]$ -----------(11)

Since conc of Ru(III) is too low to be included so it can be taken as unity.

$\text{Rate} = \frac{2 K_1 K_2 K_3 [Ru] [PA][CAT]_T}{[TsNH_2][OH^-] + K_1 [OH^-] + K_1 K_2 [PA]}$

The above equation is based on the observed kinetic orders with respect to each reactant of the reaction and is in conformity with the derived rate law.

CONCLUSION

The reaction between CAT- PA has been carried out NaOH medium. The reaction stoichiometry of 1:2 (PA:CAT) involving the oxidation of PA by CAT has been observed. Quinone oxime has been identified as the reaction product. The effect of dielectric constant and halide ion on the reaction was studied. HOCl was found as the reactive species of Chloramine-T in basic medium. From the Arrhenius plots the thermodynamic parameters have been computed and a mechanism has been proposed which was in conformity with the observed rate law.

ACKNOWLEDGEMENT

We would like to thank our Head of Department Prof. R.N. Pathak for all the facilities and support which encouraged us during our research work. We would also like to thank our colleagues and anonymous reviewer and editor for their critical and useful comments which refined the manuscript a lot.

REFERENCES

1. J. P. Polson, W. M. Lee, Hepatology., 2005**;** 41: 1179–97.
2. G. A. Ostapowicz, R. J. Fontana, F. V. Schiodt, Ann. Intern. Med., 2002**;** 137: 947–954.
3. M.Little, L. Murray, D.McCoubrie, and F.Daly, A potentially fatal prescribing error in the treatment of paracetamol poisoning, Medical J. of Australia., 2005; 183: 535-36.
4. Mulla RM, Gurubasavaraj HM. Appl Catal A Gen., 2006; 314: 208., Cross Ref.
5. Sirsalmath Kiran T, Hiremath Chanabasayya V, Nandibewoor Sharanappa T. Appl Catal A Gen., 2006; 305: 79 CrossRef.
6. Kiran TS, Hiremath DC, Nandibewoor ST. Z Phys Chem., 2007; 221: 501.
7. S. O. Adejo, R. A. Wuana, S. G. Yiase, and M. M. Ekwenchi, Kinetics of the dichromateion oxidation of simple aliphatic aldehydes. Int'l J. of Chemistry., 2008; 18(2): 63-70.
8. P.O. Baralles, R.P. Weigand, and A. M. Dias, Simultaneous determination of paracetamol and caffeine by flow injection-solid phase spectrometry using C18 silica gel as a sensing support, *Analytical Sci. J*., 2002; 18: 1241-1246.
9. Veeraiah, M.K., Ananda Murthy, A.S., and Made Gowda, N.M., Oxidation of n-propylamine and n-butylamine by chloramines-B and chloramine-T in basic medium: A kinetic study, Synth. React. Inorg. Met.-Org. Nano- Met. Chem., 2010; 40(4): 225-230.
10. Mahadevappa D.S., Ananda S., Murthy A.S.A. and Rangappa K.S., Oxidation of dimethylsulphoxide by sodium m-bromobenzene- sulphonamide: A kinetic and mechanistic study, Tetrahedron, 1984; 40(10): 1673.
11. Kolachana V. S. K, Cholkar K, Kayani W. M, Kouassi G. K, Jagadeesh R. V and Made Gowda N. M, Oxidative conversion of lactic acid by chloramine-T in sulfuric acid medium: a kinetic and mechanistic study, American Journal of Organic Chemistry., 2012, 2(1): 18-24.
12. Singh Ajay, Negi Reena, Jain Bhavana, Katre Yokraj, Surya P. Sharma, Virandr(Kinetics and Mechanism of Ru(III)-Catalyzed Oxidation of Paracetamol by Chloramine-T in Aqueous Acidic Medium), 2009; Catalysis Letters- 1/2, 285-291.

13. Singh Ajay, Negi Reena, Jain Bhavana, Katre Yokraj, Surya Prakash sisngh, Virandr. K.(Pd(II) Catalyzed Oxidative Degradation of Paracetamol by Chloramine-T in Acidic and Alkaline Media). American Chemical Society; 2011; 50(14): 8407-8419.
14. Aftab Aslam, Abdullah Asiri, Naved, Malik, Anish, Abdulrahman**(**Kinetics and Mechanistic Investigation of Decarboxylation for the Oxidation of Levofloxacin by Chloroamine-T in Acidic Medium**)** American Chemical Society, 2012; 51(13): 4819-4824.
15. T. Demappa and S.Ananda(Kinetics and mechanism of Oxidation of Methionine by Chloramine-T in Alkaline Medium in presence of OsO4 Catalyst).Asian Journal of Chemistry, 2009; 11/2: 376-383.
16. Gowda Ramachandrappa, Diwya, Iyengar Pushpa (Oxidation of Propanolol using Chloramine-T in HClO4 medium: A Kinetic and Mechanistic Study) International Research Journal of Pharmacy, 2012; 3(6): 122-125.
17. Hiremath CV, Kiran TS, Nandibewoor ST. J Mol Catalysis A Chem., 2006; 248: 163.
18. Aftab Aslam, Anish Khan,Abdulla Ansar, Naved Azum, Malik Abdul **(**Micro concentrations of Ru(III) used as homogenous catalyst in the oxidation of levothyroxine by N-bromosuccinimide and the mechanistic pathway**).**Journal of Taiwan Institute of Chemical Engineers, 2014; 45/1: 127-133.
19. Feig F. Spot Tests in organic analysis, 5th ed. Elsevier, Amsterdam, 1956; 376.