KINETIC AND MECHANISTIC STUDY OF OXIDATION OF ATENOLOL BY CERIUM (IV) IN SULPHURIC ACIDIC MEDIUM

Fadnis G Anand[1] and Agarwal Rashmi*[2]
[1]SCM Institute of Professional Studies, Indore, India
[2]Department of Pharamaceutical Chemistry, Govt. Holkar Science College, Indore, India

*Email: rasha_75@rediffmail.com

ABSTRACT
The kinetics of oxidation of antihypertensive drug, atenolol by cerium (IV) in sulphuric acidic medium has been studied spectrophotometrically at 360 nm. The reaction between cerium (IV) and atenolol in acidic medium has exhibited 2:1 stoichiometry. The order of the reaction with respect to atenolol has been found to be one. The observed pseudo first order rate constants k_{obs} increased with sulphuric acid and hydrogen ion concentrations where as decreased bisulphate ion concentration indicating the formation bisulphato reactive species of cerium (IV) in the present reaction. The thermodynamic parameters have been evaluated from the temperature variation kinetic data. A possible mechanism is proposed which has been validated by derived rate law. An attempt has been made to use rate data for kinetic estimation of atenolol.
KEYWORDS: Oxidation of Atenolol, Kinetic determination, Mechanism of oxidation: Cerium (IV) red-ox reactions

INTRODUCTION
Atenolol (ATN) (4-(2-hydroxy-3-isopropylaminopropoxy) Phenylacetamide) is a β adrenoreceptor blocking agent commonly used as antihypertensive drug[1]. It is also used in anti-angina treatment, to relieve symptoms, improve tolerance and as an anti-arrhythmic to regulate heartbeat. It is also used in management of alcohol withdrawal, in anxiety states, migraine, hyperthyroidism and tremors[2]. The European Pharmacopoeia[3] described titremetric method for the quantitative determination of atenolol where as British Pharmacopoeia[4] described spectrophotometric methods for its determination.

Earlier the kinetics of oxidation of this drug have been studied with other oxidants which include $KMnO_4$[5], chloramines T[6], chloramines B[7] diperiodato nickel(iv)[8] hexacyanoferrate(iii)[9], diperiodatoargentate Ag(III)[10] and diperiodatocuprate(II)[11] mostly in alkaline medium using Ru(III) catalyst.

Cerium (IV) is one of most important one equivalent oxidants in acidic medium which has been used in numerous kinetic and mechanistic and analytical studies including that of monosaccharides[12]. The present study deals with the kinetic and mechanistic details of oxidation of atenolol by cerium (IV) in sulphuric acid medium along with preliminary results of kinetic cerimetric estimation of atenolol using present rate data.

MATERIALS AND METHODS
Material: Commercially available chemicals of pure quality were used without further purification .A stock solution of atenolol (IPCA Laboratories Ltd., Ratlam) was prepared by dissolving appropriate amount of sample in double distilled water. Ce(IV) stock solution was prepared by dissolving ceric sulphate (99.9%Loba chem.) in aqueous sulphuric acid.
Kinetic Measurements: The kinetics was followed under pseudo first order condition where [Atenolol]and [H_2SO_4] » [Cerium(IV)] at 23± 0.1ºC. The reaction was initiated by mixing atenolol to cerium(IV) containing required concentration of sulphuric acid and the progress of reaction was followed spectrophotometrically by monitoring the decrease in absorbance at 360nm (λ_{max} for Cerium(iv)) using UV/Visible spectrophotometer Systronics-104. The pseudo rate constants, 'k_{obs}' were determined by using integrated form of first order equation and also from the regression equation applied to log(absorbance) VS time plots.

RESULTS AND DISCUSSION
The reaction mixture containing an excess of Atenolol concentration over cerium (IV) was mixed in presence of 0.7 $moldm^{-3}$ H_2SO_4 adjusted to a constant ionic strength of 0.7$moldm^{-3}$. The results indicated that two moles of cerium (IV) was consumed by one mole of atenolol(2:1) according to equation (1).

$C_{14}H_{22}N_2O_3 + 2Ce\,(IV) + 2H_2O \rightarrow C_{10}H_{10}O_5 + C_4H_{11}N + NH_3 + 2Ce\,(III) + 2H^+ \dots (1)$
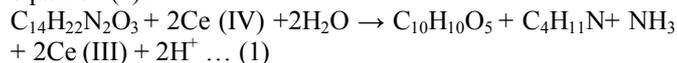
The formation of ammonia and N-isopropylmethylamine and intermediate free radical were confirmed by the procedure adopted in earlier report.[13]

The decrease in absorbance at 360nm with time uniformly followed first order kinetics uniformly in each kinetic run. The variations of pseudo order rate constant k_{obs} (sec^{-1}) with changing initial concentrations of cerium(IV),the atenolol and sulphuric acid are given in the table-(1) along with the regression equations obtained from the log-log plots. The results show first order dependence on each atenolol and sulphuric acid concentrations as evident from the slope values of 1.048 and 0.881 obtained from the respective log-log plots. The k_{obs} (s^{-1}) showed an increase with hydrogen ion concentrations at constant bisulphate ion concentrations where as decrease with bisulphate ion concentrations at constant hydrogen ion concentrations with slope values of respective log-log plots as 0.924 and- 0.983 (fig.1&2) .The variations of k_{obs} (s^{-1}) with the temperature along with thermodynamic parameters are given in table (2).

These results can now be explained on the basis of reactive species of cerium(IV) formed acid oxidation reaction steps under the present experimental conditions.
Cerium (IV) exists in various species depending on acid type, its concentration range and an attempt has been made to estimate atenolol using rate data of variation of $k_{obs}(s^{-1})$

atenolol concentration table (1)) by employing constant time and constant absorbance method using earlier nature of substrates involved in v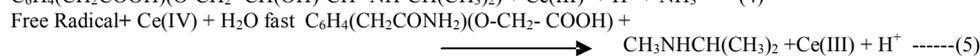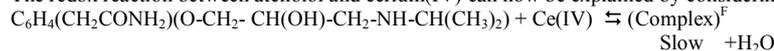arious kinetic studies . The primary reactive species of Cerium (IV) in sulphuric acid can be considered to be $Ce(SO_4)_2$ which is modified according to following as :

$Ce(SO_4)_2 + H_2SO_4 \leftrightarrows H_2Ce(SO_4)_3$ ---------(2)
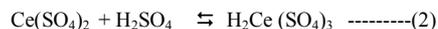
The sulphate species formed in step 2 can alternatively formed by considering the dependence of rate on bisulphate and hydrogen ion concentrations as:

$Ce(SO_4)_2 + H_2SO_4^- \leftrightarrows H_2Ce(SO_4)_3^- + H^+ \leftrightarrows H_2Ce(SO_4)_3$ ---------(3)
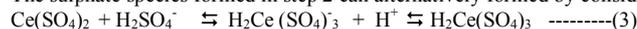
The redox reaction between atenolol and cerium(IV) can now be explained by considering following mechanistic steps:

$C_6H_4(CH_2CONH_2)(O-CH_2-CH(OH)-CH_2-NH-CH(CH_3)_2) + Ce(IV) \leftrightarrows (Complex)^F$

Slow $+H_2O$

$C_6H_4(CH_2COOH)(O-CH_2-CH(OH)-CH^\bullet-NH-CH(CH_3)_2) + Ce(III) + H^+ + NH_3$------(4)

Free Radical+ $Ce(IV) + H_2O$ fast $C_6H_4(CH_2CONH_2)(O-CH_2-COOH) +$

$\longrightarrow$ $CH_3NHCH(CH_3)_2 + Ce(III) + H^+$ ------(5)

CONCLUSION

The present study described is a simple and sensitive kinetic spectrophotometric method for the determination of atenolol. Based on the results obtained, it is found that the proposed method of estimation is accurate, precise, reproducible and economical and can be employed for routine analysis of atenolol. The popularity of reaction rate method in chemical analysis is indicated by the variety of methodologies that have been developed and appeared in many review articles and research papers as well as in some books.

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Table 1: Variation of $k_{obs}(s^{-1})$ with initial concentrations of Cerium(IV), atenolol and Sulphuric acid

Temp.=296K λ = 360nm

10^4[Ce(IV)]moldm^{-3}	10^3[Atenolol] moldm^{-3}	[H$_2$SO$_4$] moldm^{-3}	10^4 k_{obs} (s^{-1})
1.875	2.5	0.7	7.3
2.5	2.5	0.7	9.84
3.125	2.5	0.7	11.3
3.75	2.5	0.7	13.3
4.375	2.5	0.7	15.3
5	2.5	0.7	17.3
2.5	2.5	0.7	9.84
2.5	3.125	0.7	12.5
2.5	3.75	0.7	15.2
2.5	4.375	0.7	17.7
2.5	5	0.7	20.4
2.5	5.625	0.7	23.1
2.5	6.25	0.7	25.7
2.5	6.875	0.7	28.4
2.5	7.5	0.7	31.6
2.5	2.5	0.45	7.3
2.5	2.5	0.7	9.84
2.5	2.5	0.95	12.7
2.5	2.5	1.2	16.3
2.5	2.5	1.45	20.5
2.5	2.5	1.7	22.4
2.5	2.5	1.95	25.5

$\log k_{obs} = 0.857 \log[Ce(IV)] + 0.635$ ($R^2 = 0.996$)

$\log k_{obs} = 1.048 \log[Atenolol] + 0.576$ ($R^2 = 0.999$)

$\log k_{obs} = 0.881 \log[H_2SO_4] + 1.147$ ($R^2 = 0.992$)

Table 2: Thermodynamic Parameters

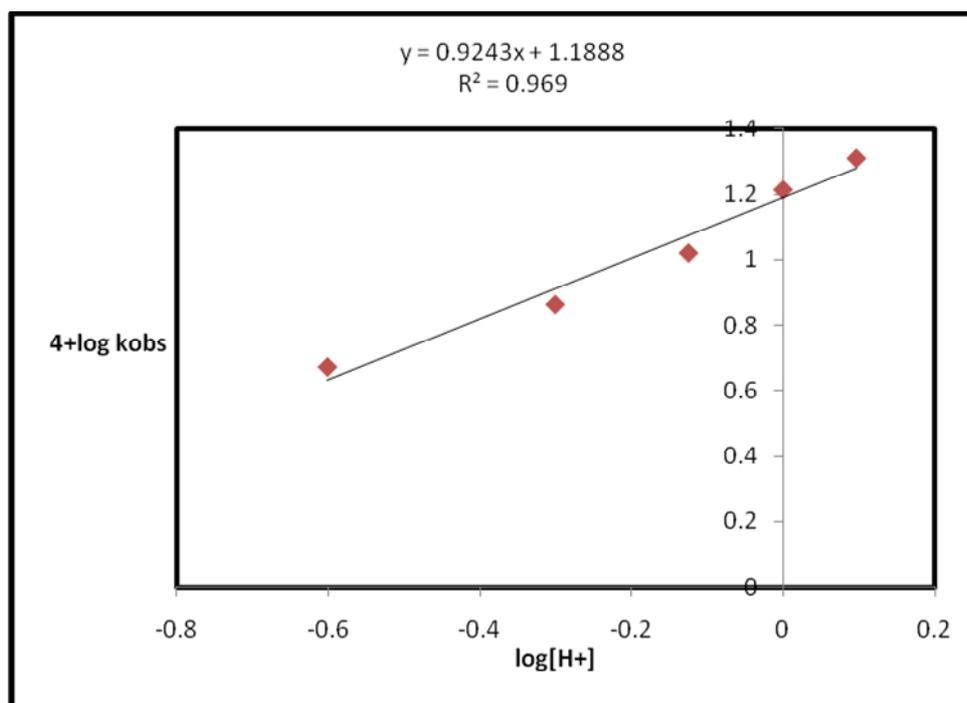| Temperature in absolute K	$10^{-4}k$ obs.	E_a K.J.mol^{-1}	$\Delta H^{\neq}$ K.J.mol^{-1}	$\Delta G^{\neq}$ K.J.mol^{-1}	$\Delta S^{\neq}$ K.J.mol^{-1}
291	6.68	62.31	59.89	46.51	-139.28
296	9.64	62.49	60.02	46.46	-136.69
301	11.97	62.99	60.49	46.75	-135.22
306	16.7	63.19	60.65	46.98	-132.9
311	21.28	63.61	61.02	46.89	-131.17
316	27	63.99	61.37	47.06	-129.53
AVERAGE	15.545	63.09±0.3	60.57±0.3	46.77±.16	-134.13±1.9'

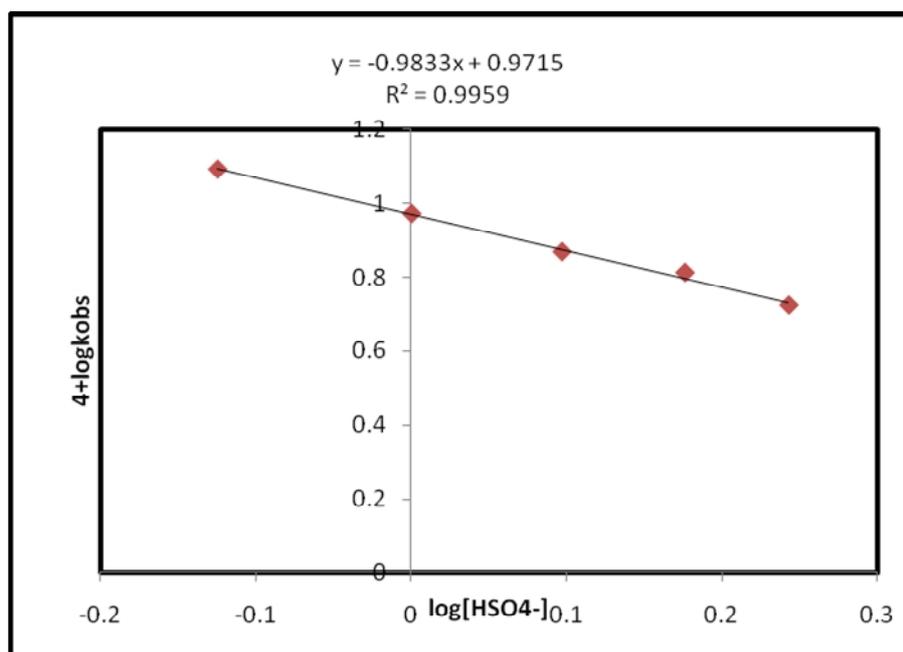Fig.1- VARIATION OF k_{obs} WITH [H$^+$] CONCENTRATION AT CONSTANT [HSO$^-_4$]

Fig.2- VARIATION OF k_{obs} WITH [HSO$_4^-$] ION CONCENTRATION AT CONSTANT [H$^+$]