Kinetics and Mechanism of Oxidation of Labetalol by Hexacyanoferrate(III) in Alkaline Medium

Engineering

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ABSTRACT *Kinetics and oxidation of labetalol (LBT) by hexacyanoferrate(III) has been studied in sodium hydroxide medium at 30 0C. The reaction was followed spectrophtometrically at λmax=420 nm. The reaction shows first order dependence on each [HCF(III)], [labetalol] and fractional order in [OH-]. It was found that the rate of the reaction increases with increase of [OH-]. The oxidation products of the reaction were found to be 1-Methyl 3-phenylpropylamine, 2-hydroxy,5-formylbenzamide and formaldehyde. A suitable mechanism involving the formation of an intermediate is proposed. The activation parameters of the reaction were computed using the linear least squares method and the values of Ea and ΔS# are found to be 69.04 ± 2.0 kJmole-1 and -314.43 ± 3.2 JK-1mole-1 respectively.*

INTRODUCTION

Labetalol [5-[1-hydroxy-2-(1-methyl-3-phenylpropylamino) ethyl] salicylamide is the first adrenergic antagonist capable of blocking both α and β receptors used in the treatment of several diseases like hypertension, angina, acute myocardial infarction, supraventicular tachycardia, ventricular tachycardia, congestive heart failure and prevention of migraine headaches. Although there were recent studies on the determination methods involving oxidation of β-blockers over the past few years, the detailed investigations on the kinetics and mechanism of oxidation of labetalol, a potent drug for the regulation of blood pressure has met only a limited attention [1-3] and relatively less information is available in the literature about their oxidation kinetics. Hexacynoferrate(III) [HCF(III)] has been widely used to oxidize numerous organic and inorganic compounds in alkaline medium[4-8]. In view of this a detailed investigation is carried out on the kinetics and mechanism of the oxidation of labetalol by alkaline hexacyanoferrate(III), spectrophotometrically at 30±0.10C.

Experimental
Apparatus

The absorbance measurements were made by using Systronics UV-Visible double beam spectrophotometer-2203 with 1cm glass cells. The temperature was maintained constant using a KEMI (India) constant temperature water bath with shaker.

Materials and reagents

All chemicals used in this investigation were of analytical reagent grade. Double distilled water was used throughout the investigation.

A 0.0109 mol dm-3 solution of labetalol (Sun pharmaceuticals) was prepared by dissolving required amount of drug in doubled distilled water.

A 0.015 mol dm-3 solution of HCF(III) (E.Merck) was prepared by dissolving requisite amount potassium hexacyanoferrate(III) in doubled distilled water and standardized by measuring absorbance using Systronics UV-Visible double beam spectrophotometer-2203 at 420nm(€=1060±50 dm-3 mol-1cm-1). Sodium hydroxide (merck, 1.0M) stock solution was prepared in doubled distilled water. Solution of desired concentration is prepared from this stock by suitable dilution. Sodium perchlorate solution is used to maintain ionic strength.

The reaction was initiated by mixing a calculated amount of HCF(III) to a mixture of labetalol(LAB), sodium hydroxide and sodium perchlorate at a constant temperature of 30 ± 0.1°C. The progress of the reaction was followed by measuring the absorb-ance of HCF(III) at 420 nm using Systronics UV-Visible double beam spectrophotometer-2203 with 1cm glass cells.

Results and discussion

A known excess of HCF(III) was made to react completely with a known amount of labetalol at 300C and in 0.01mol dm-3 sodium hydroxide. After 24 hours the residual [HCF(III)] in each case was determined spectrophotometrically at 420nm. The stoichiometry of the reaction was found to be corresponding to the equation.

$$C_{19}H_{24}N_2O_{3} + HCF(III) \rightarrow C_{10}H_{15}N + C_8H_7NO_2 + HCHO + HCF(II)$$

The product analysis has been carried out under the experimental conditions employing [labetalol] excess over [HCF (III)] and the products were identified to be (1) 1-Methyl 3-phenylpropylamine, (2) 2-hydroxy,5-formylbenzamide and (3) formaldehyde. The products 1&2 were confirmed by IR spectrum (Fig.1) by extracting the product into ether and the isolated compound was analyzed by IR spectral studies. Formaldehyde was confirmed by chromotropic acid test [9].
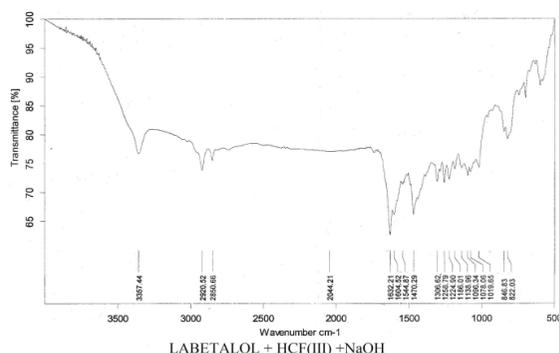
Fig:1. IR Spectrum

Main IR Bands: 3357(s) N-H; 2920-2850(s); 2044 (s) CΞN; 1632 C=O; 1604 C=C; 1450-1150(b) C-H ;1230-1010(s) C-N; 846-822 mono and di-substituted benzene.

The above bands in the Ir- spectra, there is a missing band at 3524 indicates a missing of O-H stretching which explains the oxidation of alcohol, and the peak at 1632 confirms this and this is probably aromatic aldehyde. The bands at 3357, 2920, 2850 corresponds to stretching vibrations of N-H in amine and C-H in alkyl groups. The region between 1450-1150 and 1230-1010 ascribes the bending vibrations of C-H in alkyl and C-N stretch-

ing vibrations in primary amine.

[HCF(III)] was varied from 1.0 to 6.0×10^{-4} mol dm^{-3} keeping the concentration of all other species constant, the log(absorbance) versus time plots at different concentrations of HCF(III) were found to be good straight lines parallel to one another and the pseudo first order rate constants, k' determined from the slopes of these plots were found to be invariable indicating the order with respect to [HCF(III)] to be one (Table 1).

In order to find out the dependence of rate on [LBT], kinetic runs were carried out varying the [LBT] from 1.0x10-3 to 6.0x10-3, keeping the concentration of all other species constant. The pseudo first order rate constants (Table1) were found to be increased with increase in the concentration of LBT. Further, the plot of k' versus [LBT] is a straight line passing through the origin indicating that the order with respect to [LBT] to be one. To know the effect of [OH-] on the rate of the reaction, kinetic runs were carried out keeping the concentrations of all other reactants constant and varying [OH-] with sodium hydroxide from 0.5 to 4.0x10-2 mol dm-3. The data presented in table 1 shows that the rate of the reaction increases with increase in [OH-]. Further the plot of log k vs log [OH-] is found to be a straight line with slope 0.714 indicating fractional order dependence on [OH-] (Fig 2).

Ionic strength variation studies were carried out by varying the concentration of NaClO$_4$ and keeping the concentration of all other reactants constant. (Table 1) From the perusal of the data, it was found that ionic strength has negligible effect on the rate of the reaction.

The effect of temperature on the rate of the reaction was studied by carrying out the reaction at four different temperatures 25, 30, 35, and 40^{0}C. The energy of activation E$_a$ and the entropy of activation $\Delta S^{\#}$ were calculated employing linear least squares method and were found to be 69.04 ± 2.0 kJ mole^{-1} and -314.43 ± 3.20 JK-1mole^{-1}.

Table 1: Effect of [HCF(III)], [LBT] [OH-] and μ on the pseudo first order rate constant, K' at 30±0.1^{0}C

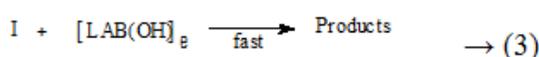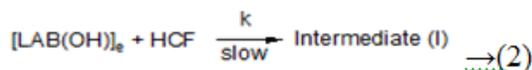| [HCF(III)] x10^{-4} (mol dm^{-3})	[LBT] x 10^{-3} (mol dm^{-3})	[NaClO$_4$] x10^{-2} (mol dm^{-3})	[OH-]x10^{-2} (mol dm^{-3})	K^I x10^{-4} (s^{-1})
1.00	4.00	2.00	1.00	10.462
2.00	4.00	2.00	1.00	10.663
3.00	4.00	2.00	1.00	10.965
4.00	4.00	2.00	1.00	9.030
5.00	4.00	2.00	1.00	8.224
6.00	4.00	2.00	1.00	8.955
4.00	1.00	2.00	1.00	2.952
4.00	2.00	2.00	1.00	4.428
4.00	3.00	2.00	1.00	6.853
4.00	4.00	2.00	1.00	9.030
4.00	5.00	2.00	1.00	13.43
4.00	6.00	2.00	1.00	15.99
4.00	4.00	1.50	1.00	9.023
4.00	4.00	2.00	1.00	9.030
4.00	4.00	2.50	1.00	9.034
4.00	4.00	3.00	1.00	9.038
4.00	4.00	3.50	1.00	9.039
4.00	4.00	4.00	1.00	9.04
4.00	4.00	2.00	0.50	5.644
4.00	4.00	2.00	0.70	6.716
4.00	4.00	2.00	1.00	9.030
4.00	4.00	2.00	2.00	19.19
4.00	4.00	2.00	3.00	25.58
4.00	4.00	2.00	4.00	27.41

Fig 2: Plot of log kI vs log [OH-]
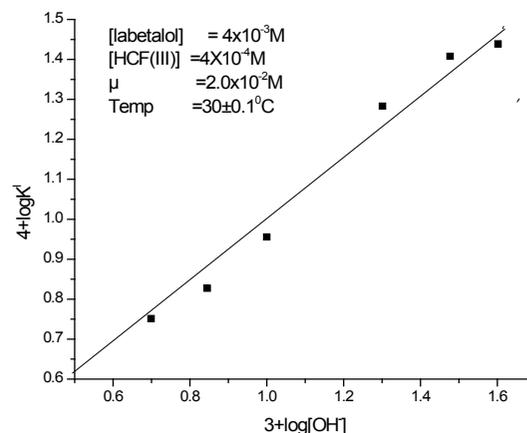
(order with respect to [alkali])

Basing on the experimental observations and the data given in table 1 the following conclusions were drawn.

1) The reaction is first order dependence on [HCF(III)]
2) The order of the reaction with respect to [LAB] is found to be unity
3) The reaction is fractional order dependent on [OH-]

In view of the above observations a plausible mechanism has been proposed.

$$LAB_\ominus + OH^- \xrightleftharpoons{K} [LAB(OH)]_\ominus \rightarrow (1)$$

$$[LAB(OH)]_\ominus + HCF \xrightarrow[slow]{k} Intermediate\ (I) \rightarrow (2)$$

$$I + [LAB(OH)]_\ominus \xrightarrow{fast} Products \rightarrow (3)$$

$$Rate,\ r = k[LAB(OH)e]\ [HCF(III)] \rightarrow (4)$$

which leads to the rate equation

$$r = \frac{Kk[LAB]_t[OH^-][HCF\ (III)]}{1 + K[OH^-]} \rightarrow (5)$$

Further

$$\frac{rate}{[HCF\ (III)]} = \frac{Kk[LAB]_t[OH^-]}{1 + K[OH^-]} \rightarrow (6)$$

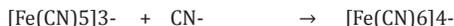Taking reciprocal of the equation (6)

$$\frac{1}{k'} = \frac{1}{Kk[LAB][OH^-]} + \frac{1}{k[LAB]} \rightarrow (7)$$

which predicts the plot of $\frac{1}{k'}$ vs $\frac{1}{[OH^-]}$

to be a straight line with a positive intercept. Exactly similar plot was obtained experimentally supporting the above mechanism proposed [Fig:3]. Further the k and K values were calculated from the intercept
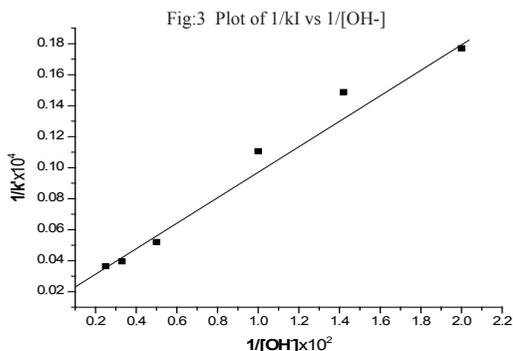
$$\left(\frac{1}{k[LAB]}\right) \text{ and solpe } \left(\frac{1}{kK[LAB]}\right)$$

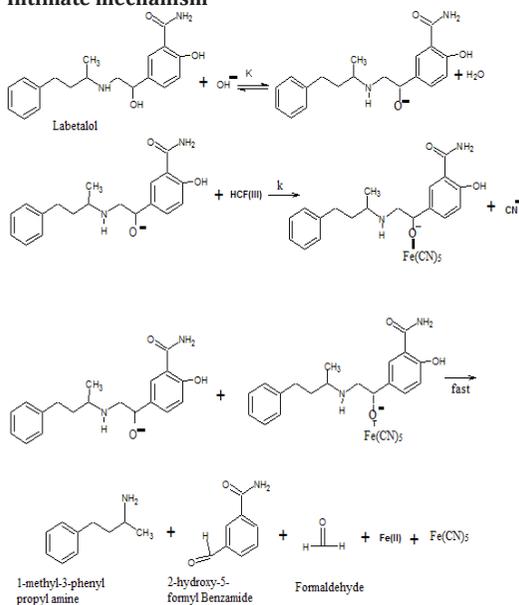of the plot and were found to be 10.4166×10^3 min^{-1} and 0.30003 respectively.

$$[Fe(CN)5]3- \quad + \quad CN- \qquad \rightarrow \quad [Fe(CN)6]4-$$

Fig:3 Plot of 1/kI vs 1/[OH-]

Intimate mechanism

Labetalol

1-methyl-3-phenyl propyl amine

2-hydroxy-5-formyl Benzamide

Formaldehyde

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