OXIDATION OF LEVOSALBUTAMOL BY KEGGIN TYPE 12 TUNGSTOCOBALTATE (III) IN AQUEOUS ACIDIC MEDIUM: A KINETIC APPROACH.

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ABSTRACT:

The kinetics and mechanism of oxidation of asthmatic drug Levosalbutamol and Keggin type 12-tungstocobaltate (III) in acidic medium was studied spectrophotometrically. The reaction between Levosalbutamol and 12-tungstocobaltate (III) in aqueous acidic medium exhibits 1:2 stiochiometry. The reaction was studied spectrophotometrically at 624 nm under pseudo-first order conditions at constant temperature $25\pm0.2^{o}C$. The main oxidative product was identified by spot test, IR, ^{1}H NMR, LC-Mass and M. P. The effect of H^{+} ion and ionic strength of the reaction medium have been investigated. The reaction constant involved in the different steps of the mechanism are calculated. The activation parameters with respect to slow step of the mechanism are computed and discussed. A mechanism related to this reaction is proposed.
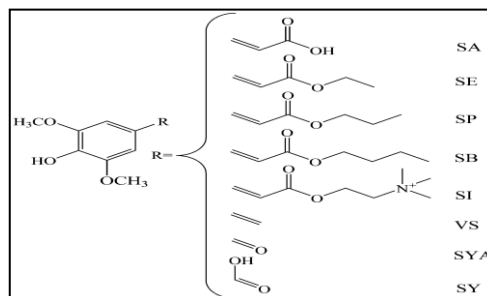
KEY WARDS:- Kinetics, mechanism, Levosalbutamol drug, 12-tungstocobaltate(III)

GRAPHICAL ABSTRACT
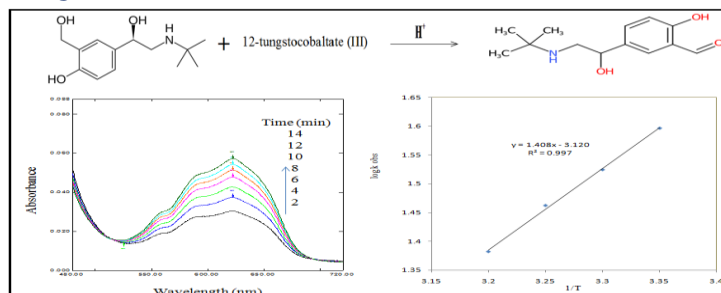
INTRODUCTION:

Heteropolyacids (HPAS) are widely used as homogeneous and heterogeneous catalyst due to their high thermal stability, strong acidity and strong oxidizing ability [1]. Many polyoxometalates exhibits biological activity [2] and antiviral activity of polyoxometalates was reported as early as 1971 by Raynaud et al [3]. Further studies by different researchers showed the effectiveness of these polyoxometalates against several viruses such as vesicular, stomatitis, polio, rubella, rauscher leukemia, rabies etc [3]. The first direct measurements of self exchange rates for electron transfer between POM anions in water using $[Co^{II}W_{12}O_{40}]^{6-}$ and its one electron oxidized derivative $[Co^{III}W_{12}O_{40}]^{5-}$ was first reported by Weakly et al and they used as POM as oxidant both for organic and inorganic substrates [5]. The potential utility of $[Co^{III}W_{12}O_{40}]^{5-}$ was used as a well defined probe for determining the nature of outer-sphere oxidations of alkyl aromatic hydrocarbons [6]. When cobalt is complexed with polytungstate ions $[Co^{III}W_{12}O_{40}]^{5-}$ / $[Co^{II}W_{12}O_{40}]^{6-}$, it was attributed to the distribution of the charge density of the cobalt ion over a large area. The complexes of transition metal ions with polyoxoanions like polytungstates are well known outer-sphere electron transfer reagents [7]. The redox reaction of $[Co^{III}W_{12}O_{40}]^{5-}$ have been recently reviewd [4,5]. Among the various heteropolyacids, the structural classes the Keggin type heteropolyacids have been widely used as homogeneous and heterogeneous catalysts for acid-base and oxidation reactions [8]. Levosalbutamol is a short acting asthmatic drug used in the treatment of asthma and chronic obstructive pulmonary disease (COPD). It is marketed under the brand name xopenex. The drug is R- enantiomer of its prototype drug salbutamol or albuterol. It is available in generic formulation by pharmaceutical companies including Cipla, Teva and Dey. Its molecular formula is $C_{13}H_{21}NO_3$ and its appearance is white to off white crystals. A large clinical study demonstrated that inhaled levosalbutamol, 0.125 mg three times daily, provides effective relief from the symptoms of asthma [9].

EXPERIMENTAL
## CHEMICALS AND MATERIALS

All chemicals used were of analytical reagent grade and double distilled water was used throughout the work. The solution of levosalbutamol was prepared by dissolving the requisite amount of it in double distilled water. The solution of perchloric acid was prepared and standardized against standard sodium hydroxide.

KINETIC MEASUREMENTS

The kinetic measurements were performed on visible spectrophotometer (model EQ-823). The oxidation of levosalbutamol by 12-tungstocobaltate (III) was followed under pseudo-first order conditions at constant temperature $25\pm0.2^{o}C$. The reaction was initiated by mixing the solution of 12-tungstocobaltate (III) and levosalbutamol which also contained the required concentration of perchloric acid and sodium perchlorate to maintain acidity and ionic strength respectively. The reaction was followed by measuring the absorbance of 12-tungstocobaltate (III) and levosalbutamol at 624 nm as a function of time. Beer's law was tested for $[Co^{III}W_{12}O_{40}]^{5-}$ between the concentration of 0.25×10^{-3} and 2.5×10^{-3} mol dm^{-3} under the experimental condition.

SPECTROPHOTOMETRIC MEASUREMENT

The spectra of 12-tungstocobaltate(III) complex and the reaction mixture were recorded by using visible spectrophotometer (model EQ-823) between the wavelength rang 400-700 nm. The spectrum of 12-tungstocobaltate(III) complex in presence of 1.5 mol dm^{-3} perchloric acid in the reaction mixture soon after the mixing of reactant is shown in Fig. 1.
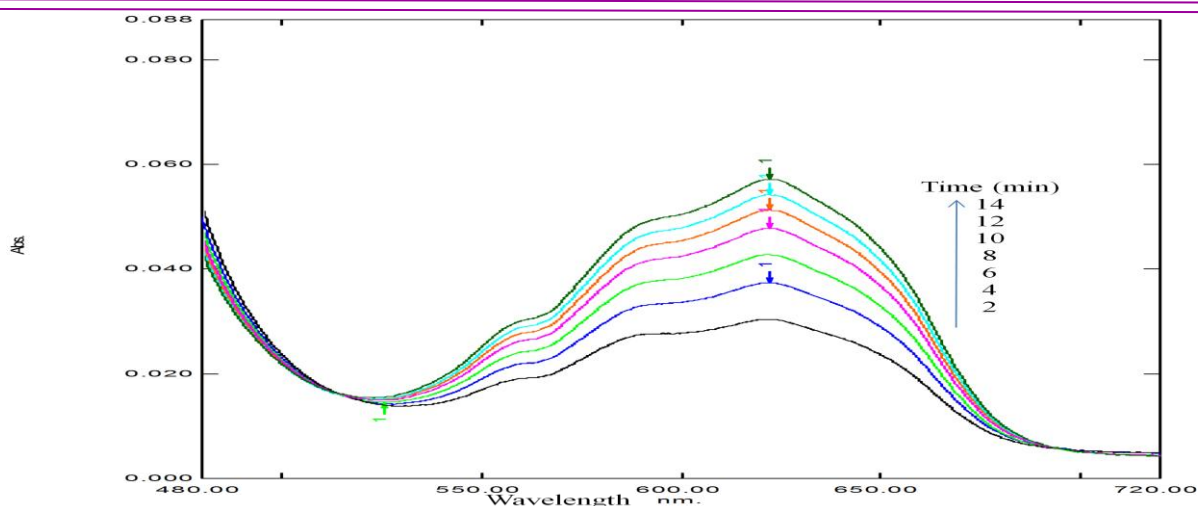
Fig-1 -Visible spectra of $[Co^{III}W_{12}O_{40}]^{5-}$ and Levosalbutamol in reaction mixture
$[Co^{III}W_{12}O_{40}]^{5-} = 0.5\times10^{-3}$mol dm^{-3}, [Levosalbutamol] $= 0.5\times10^{-2}$ mol dm^{-3}
$[HClO_4]=1.5$ mol dm^{-3} and $[NaClO_4] = 0.3$ mol dm^{-3}

RESULT AND DISCUSSION

The stoichiometry was studied by keeping the constant concentration of $[Co^{III}W_{12}O_{40}]^{5-}$ 0.7×10^{-2} mol dm^{-3} and varying the concentration of levosalbutamol from 0.3×10^{-2} to 0.5×10^{-3} mol dm^{-3} with constant concentration of 1.5 mol dm^{-3} HClO$_4$. The reaction mixtures were equilibrated at 25 ± 0.2^{o}C for 24 hours. The progress of the reaction was followed by measuring the absorbance at 624 nm for the formation of $[Co^{II}W_{12}O_{40}]^{6-}$. The results revealed that the two moles of $[Co^{III}W_{12}O_{40}]^{5-}$ consumes one mole of levosalbutamol. After completion of the reaction, 5-[2-(*tert*-butylamino)-1-hydroxyethyl]-2-hydroxybenzaldehyde was found as the product of oxidation and was identified by its 2,4-DNP derivative. The purity of the product was checked by TLC and melting point. The main oxidative product was confirmed by FT-IR specturm, which showed frequencies at 1720 cm^{-1} due to >C=O stretching of aldehyde and at 3272 cm^{-1} due to O-H stretching. ^{1}H NMR spectrum (DMSO), spectra peaks in ppm, (9H, s, δ -0.9), aldehydic group (1H, s, 9.3), NH group (1H, s, 7.0), (2H, d, 3.1) (1H, t, 7.3 benzylic carbon), (Ar 3H, 7.0 − 7.6), benzylic OH, s- 5.2. The mass spectra showed a molecular ion peak at 237 amu indicating the presence of 5-[2-(*tert*-butylamino)-1-hydroxyethyl]-2-hydroxybenzaldehyde. Further oxidation of 5-[2-(*tert*-butylamino)-1-hydroxyethyl]-2-hydroxybenzaldehyde was not observed under the present kinetic conditions.

Table 1 : Effect of [$Co^{III}W_{12}O_{40}]^{5-}$ [Levosalbutamol] and [HClO$_4$] on the oxidation of levosalbutamol by $[Co^{III}W_{12}O_{40}]^{5-}$in acidic medium at 25 ± 0.2^{o}C, I= 0.3 mol dm^{-3}

$[Co^{III}W_{12}O_{40}]^{5-} \times10^{-3}$ mol dm^{-3}	[LEVO] $\times10^{-2}$ mol dm^{-3}	[HClO$_4$] mol dm^{-3}	$k_{obs} \times10^{-3}$ sec^{-1}
0.25	0.5	1.5	3.2
0.5	0.5	1.5	3.2
0.75	0.5	1.5	3.2
1.5	0.5	1.5	3.2
2.5	0.5	1.5	3.2
1.5	0.5	1.5	3.2
0.5	0.5	1.5	3.2
0.5	0.6	1.5	3.6
0.5	0.7	1.5	4.1

0.5	0.8	1.5	4.7
0.5	0.9	1.5	5.5
0.5	1.0	1.5	6.3
0.5	0.5	1.0	0.9
0.5	0.5	1.25	1.6
0.5	0.5	1.5	2.5
0.5	0.5	1.75	3.9
0.5	0.5	2.0	4.3

REACTION ORDER

The reaction orders have been determined from the slopes of log k_{obs} versus log (concentration) plots by varying the concentration of levosalbutamol, $[Co^{III}W_{12}O_{40}]^{5-}$ and $HClO_4$ in turn while keeping other conditions constant. The effect of Levosalbutamol on the rate of reaction was studied at constant $[Co^{III}W_{12}O_{40}]^{5-}$ at 0.5×10^{-3} mol dm^{-3}, [HClO$_4$] at 1.5 mol dm^{-3} and ionic strength at 0.3 mol dm^{-3}, the substrate levosalbutamol varied in the range 0.5×10^{-2} to 1.0×10^{-2} mol dm^{-3}. The k_{obs} values increased with increase in concentration of levosalbutamol (Table 1), the order with respect to levosalbutamol was found to be unity. The constancy in k_{obs} values with increase in $[Co^{III}W_{12}O_{40}]^{5-}$ (Table 1) indicates the unity order with respect to $[Co^{III}W_{12}O_{40}]^{5-}$.

EFFECT OF HYDROGEN ION CONCENTRATION

The effect of hydrogen ion concentration on the rate of reaction was studied at constant [Levosalbutamol], $[Co^{III}W_{12}O_{40}]^{5-}$, ionic strength at 25 ± 0.2^{o}C. The effect of hydrogen ion concentration on the reaction was studied in order to understand the nature of reactant species present in the solution. The concentration of H$^+$ ion were varied between 1.0 to 2.0 mol dm^{-3} keeping all other conditions constant. It was found that the reaction rate increases with increase in concentration of H$^+$ ion as shown in Table 1. The order in H$^+$ ion was found to be 0.95, as determined from the plot of log k_{obs} versus log H$^+$ ion.

TEST FOR FREE RADICALS

The reaction was studied in presence of added acrylonitrile to understand the intervention of free radicals in the reaction [10,11,12]. To the reaction mixture, the known quantity of acrylonitrile scavenger was added initially and kept in an inert atmosphere for one hour. Then the reaction mixture was diluted with methanol which gives the precipitate suggesting there is participation of free radicals in the reaction [13].

Effect of ionic strength and solvent polarity
Effect of ionic strength

The effect of ionic strength was studied by varying the sodium perchlorate concentration in the reaction mixture. The ionic strength of the reaction medium was varied from 0.15 to 0.75 mol dm^{-3} with all other conditions being constant. It was found that as ionic strength increases, the rate of reaction decreases [14]. The plot of log k_{obs} versus $I^{1/2}$ was linear with positive slope.

Effect of solvent polarity

The relative permittivity effect was studied by varying the percentage of acetonitrile from 0 to 40 % v/v in the reaction mixture with all other conditions being constant. The relative permittivities of the reactions mixtures were computed from the values of the pure solvents. It was found that with decrease in dielectric constant of the reaction mixture, the rate of the reactions increases 15]. The plot of log k_{obs} versus (1/D) was linear with negative slope.

EFFECT OF TEMPERATURE:-

The effect of temperature on the reaction rate was studied by performing the kinetic run at four different temperatures 25, 30, 35, 40 ^{o}C by keeping other conditions constant. The rate constants were found to be increased with increase in temperature (Table 2). The energy of activation and enthalpy of activation were evaluated from the Arrhenius plot of log k_{obs} versus (1/T) (Fig. 2). The activation parameters were found to be Ea=25.13±0.2 kJ mol^{-1}, ΔH=23.614 kJ mol^{-1}, ΔG=87.374 kJ mol^{-1}, ΔS= -195.31 J K^{-1}mol^{-1}.

Table 2 Effect of temperature on rate for the oxidation of levosalbutamol by [$Co^{III}W_{12}O_{40}]^{5-}$ in acid medium.[$Co^{III}W_{12}O_{40}]^{5-}$ = 0.5×10^{-3}mol dm^{-3}, [Levosalbutamol] = 0.5×10^{-2} mol dm^{-3} [HClO$_4$]=1.5 mol dm^{-3} and [NaClO$_4$] = 0.3 mol dm^{-3}

Temperature (K)	k×10^{-3}
298	3.2
303	4.4
308	6.5
313	7.8

Figure 2 - Arrhenius plot of logk_{obs} versus (1/T).
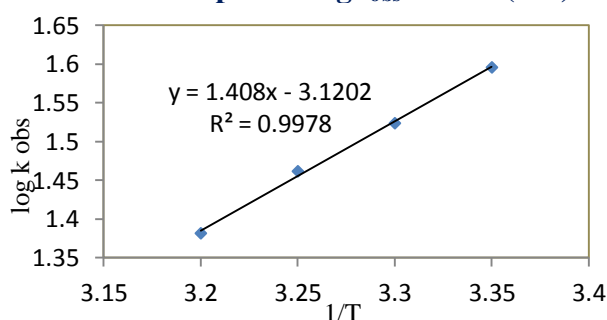
In the present study oxidation by the Co(III) complex, a well known outer-sphere oxidants [13,14] proceeds with two single-electron transfer steps. The kinetics of electron exchange between Co(II) and Co(III) complex using ^{60}Co tracer techniques reveals that tungstate groups are substitutionally inert and species of this type shows outer-sphere electron transfer reactions in solutions [16]. The reaction between levosalbutamol and [$Co^{III}W_{12}O_{40}]^{5-}$ in acidic medium has a stoichiometry of 1:2, with an order of unity for [$Co^{III}W_{12}O_{40}]^{5-}$ levosalbutamol and HClO$_4$.

First order dependence on [$Co^{III}W_{12}O_{40}]^{5-}$ concentration has observed during the reaction. No effect of the products was observed. The following mechanism has been proposed in the form of Scheme 1.
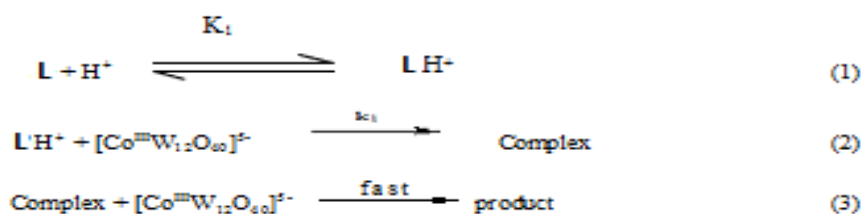
Scheme 1

L= Levosalbutamol

The protonated levosalbutamol species and unprotonated $[Co^{III}W_{12}O_{40}]^{5-}$ are active species in the reaction and gives a complex (C) in slow step. This complex reacts with second molecule of $[Co^{III}W_{12}O_{40}]^{5-}$ in the fast step to give the product.

$$\text{Rate} = \frac{K_1 k_1 \, [\,L\,]_T \, [Co^{III}W_{12}O_{40}]^{5-}}{(K_1 + [H^+]\,)} \qquad (4)$$

$$k_{obs} = \frac{K_1 k_1 \, [\,L\,]_T}{(K_1 + [H^+]\,)} \qquad (5)$$

The mechanism according to scheme 1 gives the product, 5-[2-(*tert*-butylamino)-1-hydroxyethyl]-2-hydroxybenzaldehyde. It was observed that the acid did not undergo further oxidation under the present kinetic conditions.

Kinetics of oxidation of Levosalbutamol was investigated at several initial concentrations of reactants in acidic medium. The oxidant $[Co^{III}W_{12}O_{40}]^{5-}$ was varied by keeping constant concentrations of levosalbutamol and $HClO_4$ at 25 ± 0.2ºC. The constancy in rate constant k_{obs} indicates that the unity order with respect to $[Co^{III}W_{12}O_{40}]^{5-}$. It was further supported by linear plot of log $[Co^{III}W_{12}O_{40}]^{5-}$ versus time. The values of rate constants are listed in (Table 1). Similarly, varying the concentration of levosalbutamol with all other parameters constant, the order with respect to levosalbutamol was found to be near to unity 0.90.

The effect of ionic strength and solvent polarity was studied by keeping $[Co^{III}W_{12}O_{40}]^{5-}$, levosalbutamol and $HClO_4$ at 0.5×10^{-3} mol dm^{-3}, 0.5×10^{-2} mol dm^{-3} and 1.5 mol dm^{-3}. Sodium perchlorate and acetonitrile were used to vary the ionic strength and the solvent polarity respectively. The rate of the reaction increases with increase in ionic strength. The relative permittivities of the reaction mixture were computed from the values of the pure solvent. It was found that the solvent polarity had negligible effect on the rate constant

The plot of $\log k_{obs}$ versus $1/T$ was found to be linear showing that the reaction obeys Arrhenius temperature dependence. The values of enthalpy of reaction (ΔH), entropy of reaction (ΔS) and free energy of activation (ΔG) were calculated as 23.614 kJ mol^{-1}, -195.614 J K^{-1} mol^{-1} and 87. 73 kJ mol^{-1} respectively. The values of activation parameters are in agreement with the mechanisms proposed. The positive free energy of activation indicates the transition state is highly solvated.

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