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Research Article

"MECHANISTIC INVESTIGATION OF OXIDATION OF SALBUTAMOL WITH N-CHLOROBENZAMIDE IN ACID MEDIUM: A KINETIC APPROACH"

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Abstract

Mechanistic investigation of oxidation of salbutamol with N-chlorobenzamide in acid medium has been investigated in water-HOAc medium. The reaction is of pseudo first-order in [NCB], fractional order in [SBL] and first order in [H$^+$] ion. The velocity of the reaction increases with increase the Dielectric constant of medium and solvent polarity. Effect of temperature has been studied and thermodynamic parameters are calculated and a suitable mechanism has been suggested.

Key words: **Lactic acid; Mechanistic investigation; fractional order; Di electric constant of medium; thermodynamic parameters**

INTRODUCTION

Chemical kinetics, with this view point, can be contrasted with thermodynamics which provides a static view point. Thermodynamics deals only in the initial and a final state of a system, but time is not one of the thermodynamic variables. Kinetics aims fundamentally at the details of the process in which a system converts from one state to another and the time required for the transformation[1]. Hence, chemical kinetics provides information about the rate of reaction on possible pathways, by which the reactants are transformed into products. Thus, the fundamental of objective of the study of the kinetics of chemical reaction is to unfold the mysteries of chemical processes[2-3]

N- Halo compounds, which are good sources of positive halogen in polar solvents, have been extensively employed as halogenating and oxidizing agents for organic substrate[1]. Amongst the N-chloro compound N-Chlorophthalimide[2] (NCP) has wide synthetic utility as it has the

most polar >N-X bond among the series TCIAN, N-chlorobarbitol, NCS and NBS TCICA has been used in synthetic organic chemistry as an oxidizing and halogenating reagent[4-7].

In present kinetics and mechanistic investigation N-chlorobenzamide[8-9] (NCB) choose as an oxidant to oxidized solbutamol which is a β2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease (COPD). The kinetic study of oxidation of this bioactive compound is of much use in understanding the mechanistic profile in redox reactions. Consequently, the kinetics of oxidative degradation of solbutamol (SBL) have been studied with variety oxidants as *N*-bromosuccinimide[10], NBP[11], **etc**. but no literatures are found on the same title, thus we have choose this problem to explore the kinetic task.

EXPERIMENTAL

Materials

The solution of NCB (sigma-Aldrich sample) so obtained was prepared by dissolving its weighed quantity in 100% CH_3COOH (B.D.H.) and kept either amber colored flask or black paper wrapped around it to save it from the action of diffused day light which alters appreciably its concentrations.

The standardization of NCB was done by taking one ml of its solution in conical flask to which 10 ml of 2% KI solution followed by 5ml of 2N H_2SO_4 added to it. The liberated iodine was titrated against standard sodium thiosulphate (hypo) solution using starch solution as an indicator. Salbutamol sulphate (Gift sample Medrich, India) was used as substrate for the preparation of solution. The solution of Salbutamol was prepared in requisite volume of glacial acetic acid-water mixture. Other reagents are grade chemicals and doubly distilled water was used throughout the experiments.

KINETIC STUDIES

Preliminary experiments for the oxidation of Salbutamol with N-chlorobenzamide were conducted to choose the appropriate conditions of concentration of the reactants and temperature under which these oxidation proceeds with measurable rate. It has been observed that in the presence of Perchloric acid, the oxidation of this substrate proceeds at a measurable rate. The kinetic study of each system undertaken was carried out by integration and Ostwald's isolation methods. In each set of reaction, concentration of substrate was taken in large excess over the concentration of oxidant.

PROCEDURE

The known volume of oxidant, acetic acid and perchloric acid were taken in a conical flask while substrate and rest amount of water were in another conical flask. These two-stopper flasks were placed at experimental temperature in a thermostat of sensitivity $\pm 0.1^0$C. After the equilibrium of the temperature, the both solutions were mixed and aliquot was withdrawn immediately and was quenched. The amount of un-reacted N-chlorobenzamide was estimated iodometrically with the help of standard solution of sodium thiosulphate using starch as an indicator. The titre value at zero time was taken as "a".

The aliquots were withdrawn at regular intervals and were estimated for un-reacted N-chlorobenzamide. These readings are the values of (a-x) at time "t". The experimental data were fed into the integrated form of equation for first-order reactions. The values of pseudo first-order rate constant obtained from the rate equation -

$$ k = \frac{2.303}{t} \log \frac{a}{(a-x)} $$

Were found fairly constant within the experimental error suggested that each reaction obeys first-order kinetics.

The effect of [perchloric acid] on the oxidation of Salbutamol was determined by adding different concentrations of perchloric acid. The effect of Benzamide was also investigated. Different compositions of binary solvent mixtures of acetic acid-water were used to study the effect of variation of dielectric constant of the medium.

Stoichiometry and end-product analysis: stoichiometry of the reaction was ascertained by equilibrating the reaction mixture containing an excess of N-chlorobenzamide over Salbutamol and Perchloric acid, for 24 hrs. at 308K. The un-reacted oxidant (N-chlorophthalimide) was determined by iodometrically. The estimated amount of un-reacted N-chlorobenzamide showed that one mole of Salbutamol consumes one mole of N- chlorophthalimide.

Salbutamol   3-hydroxy-4-(hydroxy
                              methyl)benzaldehyde
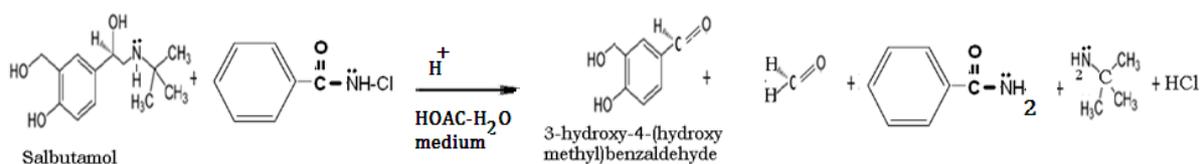
3-hydroxy-4-(1-hydroy methylene) benzaldehyde and formaldehyde were identified as the main product of oxidation which was identified by existing conventional methods [12-14].

RESULTS AND DISCUSSIONS

The experimental kinetic data have been collected for variant concentrations of oxidant (NCB) at fixed concentration of other reactants and temperature. The linear plots of log (a-x) vs. Time, suggested that the first-order rate dependency with respect to oxidant. The value of first-order rate constant evaluated from the plot is excellently in good agreement with those calculated from first-order rate equation. (Table.1)

The reaction rate increased with increase in [SBL]. Plot of k_1 versus [SBL initially linear passing through origin at low concentrations but at higher concentrations of substrate it bent to x-axis tends 1 to 0 orders. This confirmed the existence of equilibrium between solbutamol (SBL) and oxidant (NCB) and appeared before the slow step. Furthermore con-firming the fractional order dependence on [SBL]. (Fig. 2; r > 0.9745). Fractional slopes of the plots indicate a fractional order dependence on [SBL] (Fig.1, 2), this implies that, rate is proportional to [SBL]. Therefore, rate = k_1 [SBL.]$^{0.36-0.97}$. this explains that the influence of substrate concentration on the rate is low. Reaction is fully perchloric acid catalyzed and velocity of the reaction increases with increase the concentration of perchloric acid. The plot of k_1 vs. [H$^+$] is obtained linear with the positive unit slope, confirming that the reaction fully catalyzed. (Fig.3); the first-order rate constant increases with increase composition of acetic acid i.e. rate accelerated with increase in dielectric constant of the medium (Table:2). The plot of log k_1 versus 10^3/D were obtained linear with positive slope.

The reaction rate ebbs when the concentration of benzamide is added. The presence of free radicals in the system understudy was tested qualitatively by addition of 1-2 ml of acrylonitrile (monomer) in about 5-6 ml of the reaction mixture employing trapping method. The non-occurrence of turbidity and white precipitate clearly indicates the absence of free radicals in the system. Various activation parameters namely temperature coefficient, energy of activation (Ea) , frequency factor (A), enthalpy of activation ($\Delta H^{\#}$), free energy of activation ($\Delta G^{\#}$), and entropy of activation ($\Delta S^{\#}$) for each reaction are calculated for SBL–NCB system and according to the reaction mechanism, rate equation and order of reaction have been discussed.

The Arrhenius plot had been drawn between log k_1 vs. 1/T, the reciprocal of absolute temperature, the value of energy of activation (Ea) is calculated from the slope of Arrhenius plot. The frequency factor (A) computed using graphical value of Ea. The enthalpy of activation ($\Delta H^{\#}$) is evaluated from the slope of the plot between log krh/K$_B$ T vs. 1/T.

Table.1
Dependence of rate of oxidation reactions on the initial concentration of oxidant (NCB)

[SBL] : 1.25×10^{-2} (mol.dm^{-3}) ,
[H$^+$] : 1.25×10^{-2} (mol.dm^{-3})
HOAc-H$_2$O : 30% (v/V) ;
Temp. : 308 K.

[NCB]10^3(mol.dm^{-3})	$10^5 k_1$(s^{-1})
1.00	11.22
1.25	11.30
2.00	11.32
2.50	11.40
4.00	11.31
5.00	11.22

DEPENDENCE OF RATE ON THE VARIATION IN THE CONCENTRATION OF SUBSTRATE
Plot of k_1 vs. [Substrate]
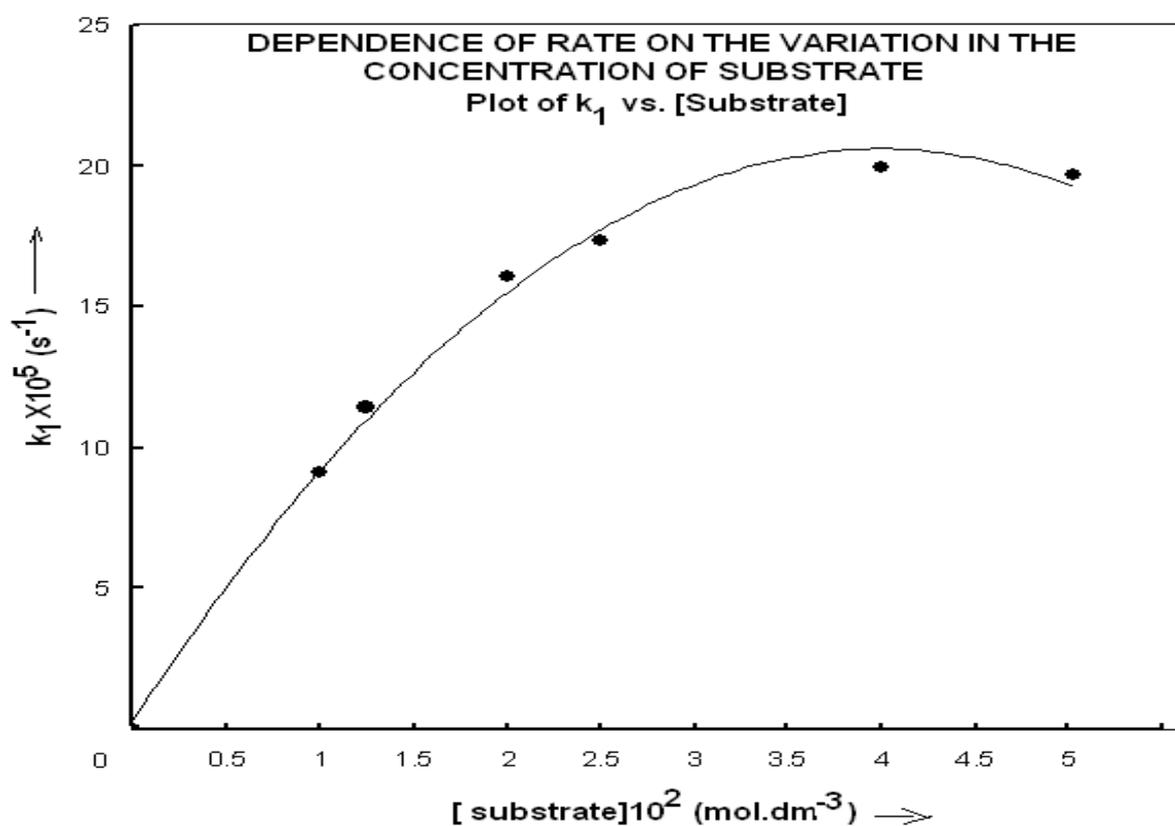
Fig.1

[NCB] : 2.50×10^{-3}(mol.dm^{-3})
[H$^+$] : 1.25×10^{-2}(mol.dm^{-3})
HOAc-H$_2$O : 30% (v/V) ;
Temp. : 308 K.

DEPENDENCE OF RATE ON THE VARIATION IN THE CONCENTRATION OF SUBSTRATE

Plot of $\frac{1}{k_1}$ (s^{-1}) vs. $\frac{1}{[\text{Substrate}]}$

$r^2 = 0.98$

Fig.2	[NCB]	:	2.50X10^{-3}(mol.dm^{-3})
	[H$^+$]	:	1.25X10^{-2}(mol.dm^{-3})
	HOAc-H$_2$O	:	30% (v/V) ;
	Temp.	:	308 K.

Table: 2

Summary: Dependence of rate on the variation of the composition of binary solvent polarity.

	[NCB]	:	2.50X10^{-3}(mol.dm^{-3})
	[SBL]	:	1.25X10^{-2}(mol.dm^{-3})
	[H$^+$]	:	1.25X10^{-2}(mol.dm^{-3})
	Temp.	:	308 K

HOAc-H$_2$O % (v/v) ;	$\dfrac{10^3}{D^{\#}}$	$10^5 k_1$(s^{-1})
20	17.17	11.261
30	19.15	11.407
40	21.98	11.572
50	25.64	11.621
60	30.36	11.732

Fig.3

[NCB]	:	2.50×10^{-3}(mol.dm^{-3})
[SBL]	:	1.25×10^{-2}(mol.dm^{-3})
HOAc-H_2O	:	30% (v/V) ;
Temp.	:	308 K.

Table: 3

THERMODYNAMIC PARAMETER

Substrate	Ea KJ mol^{-1}	A s^{-1}	$\Delta H^{\#}$ KJ mol^{-1}	$\Delta G^{\#}$ KJ mol^{-1}	$\Delta S^{\#}$ JK mol^{-1}
SBL	48.64 ±0. 89	5.34×10^3 ±0. 28	44.90 ±0. 69	-75.26 ±0.29	-79.25 ±0.76

MECHANISM

In view of the above experimental kinetic data, facts and finding, a suitable mechanism has been proposed for the oxidation of SBL – NCB system as:
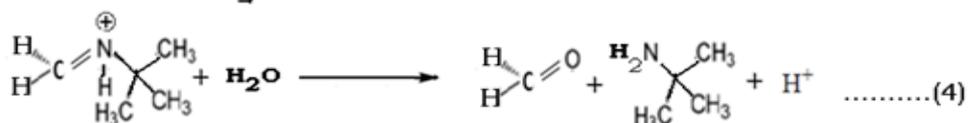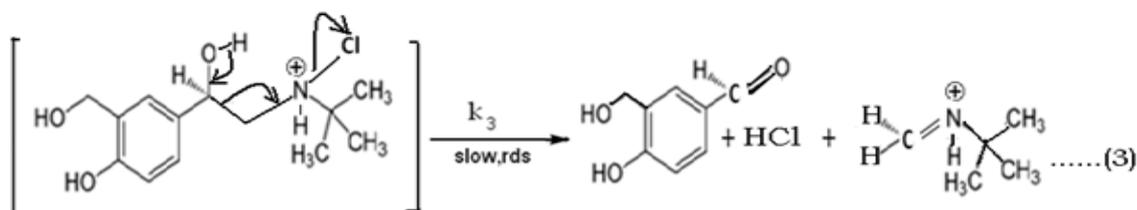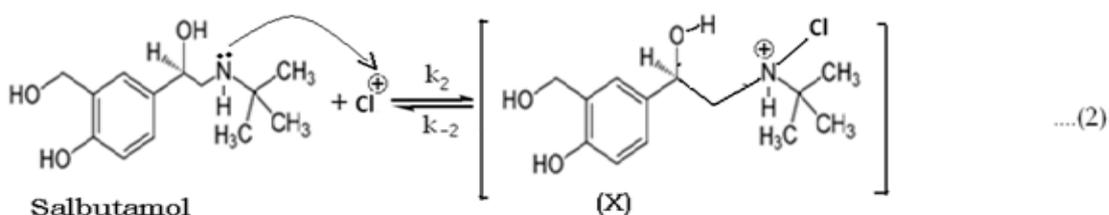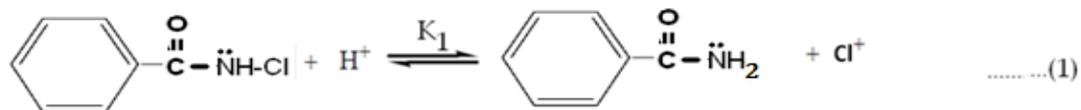
RATE LAW EXPRESSION

$$k_{obs.} = \frac{K_1 k_2 k_3 [\text{H}^+][SBL]}{[\text{NH.}]\{k_{-2} + k_3\}} ... \qquad \text{............(5)}$$

Equation (5) is in good agreement with the observed experimental data and results.

CONCLUSIONS

Kinetic studies utilizing NCB as an oxidant in series of reaction lead us to conclude that the activity of it is much limited and needs to be explored in a Broadway. It possesses vital potentiality with two-electron system and displays interesting behaviors at moderate condition of temperature. The study will act as a milestone and will pave the way for future researcher to enlighten the mechanism utilizing NCB as an oxidant for some other organic compounds like disulphide, acetophenone and substituted acetophenones, aliphatic ketones, amines and amino acids in the similar manners and also can be catalyzed by micelles like CTAB and phosphotungstic acid etc. The contribution and information through kinetic study will enrich

chemical literature to a great extent in journals. Its applied aspects may be judged in lather industries, analytical, chemical separation, and identification of organic compounds and paper and pulp industries[15-16].

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