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Research Articles

OXIDATION OF FLAVOXATE BY N-CHLOROSACCHARIN IN ACETIC ACID-WATER MEDIUM, A KINETIC AND MECHANISTIC APPROACH

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ABSTRACT:

Study of oxidation of Flavoxate (FX), a bioactive compound, with potent oxidant, N-Chlorosaccharin (NCSA) has been carried out in the presence of HCl in acetic acid -water medium, at 313 K. The experimental rate laws obtained are:-d [NCSA]/dt = k [NCSA][FX] in Acetic Acid-water medium. The reaction is fully acid catalyzed and retardation of the added Saccharin. Variation of ionic strength of the medium shows negligible effect on rate of reaction. Decrease in dielectric permittivity of the medium decreased the rate. The stoichiometry of the reaction was found to be 1:1. The oxidation products of 2-PEA were identified as the 3-methyl-4-oxo-2-phenyl-4H chromene-8-(2-acetaldehyde) carboxylate and pipiridine. The reactions were studied at different temperatures and the activation parameters have been evaluated. The reaction constants involved in the proposed mechanisms were

computed. The proposed mechanisms and the derived rate laws are consistent with the observed experimental results.

Keywords: Kinetics, N-Chlorosaccharin (NCSA), Flavoxate (FX), eco-friendly.

INTRODUCTION

A body of water on top of a hill may be described in terms of its equilibrium state. Similarly, the same body of water at some subsequent time may find its way to a lake at the bottom of the hill[1]. There are perfectly definite descriptions of both states and of the energy differences between them. However, if we try to describe the transition, the water in process of flowing from the hilltop, we see that it may depend on almost innumerable factors: on the outlets, on the contour of the hillside, on the structural stability of the contour, on the numerous subterranean channels through the hillside that may exist and permit seepage. Finally, if someone has bored a hole under the hilltop, it will take careful experimental investigation to uncover this additional factor, which will affect the flow.

In present paper we explored the kinetics of oxidation of Flavoxate[2] (2-(-1-piperidyl) ethyl 3-methyl-4-oxo-2-phenylchromene-8-carboxylate) as a substrate which is used as drug to treat spasms in the urinary tract or difficult urination and is taken in combination with antibiotics to treat the infection. Flavoxate hydrochloride, is a muscle relaxant and it works by relaxing the involuntary muscle that is found in the wall of the bladder[3]. A review of literature shows that there is only information available on the kinetics and oxidation of flavoxate by *chloramine-T (CAT)***,** however, there is no work reported on the same title, there was a need for understanding the mechanism of oxidation of flavoxate. This study may throw some light on the

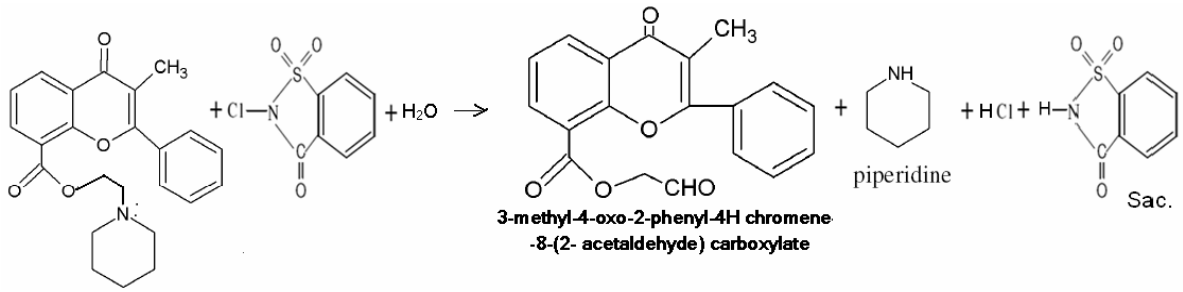
metabolic conversions in the biological system. Thus, in view of exploring the kinetics of kinetics and mechanistic aspects of the oxidation of flavoxate with particular NCSA (oxidant), in order to throw light insight the reaction path and its vital activity, we have chosen this problem first time.

The oxidant N-Chlorosaccharin (Aldrich sample), Flavoxate (Gift sample of Becon India ltd.) were used and purified by the literature procedure[4]. The standard solution of Flavoxate (sigma chemicals sample) was prepared in acetic acid. Double distilled water employed in all kinetic runs. To prevent photochemical effect, the freshly prepared solution of N-Chlorosaccharin was stored in an amber colored bottle and its strength was checked iodometrically[4] using 1 % solution of freshly prepared starch as an indicator.

Kinetic measurements*:* All kinetic measurements made under pseudo first-order conditions, by keeping large excess of Flavoxate over oxidant N-Chlorosaccharin. Mixture containing requisite amount of solutions of N-Chlorosaccharin, and HCl in 30 % acetic acid equilibrated at 313 K. To this mixture added a measured amount of pre-equilibrated at 313K., standard solution of N-Chlorosaccharin. To maintain the desired temperature (within ± 0.1^{o}C) the reaction mixture was kept in a thermo stated water bath and the progress of the reaction was monitored iodometrically by withdrawing aliquots of the reaction mixture at regular time of intervals.

Stoichiometry and Product Analysis: Stoichiometry of the reaction was ascertained by equilibrating the reaction mixture containing an excess of N-Chlorosaccharin over flavoxate and hydrochloric acid in 30 % Ac.OH for 24 hrs. at 313 K. The un-reacted oxidant (N-Chlorosaccharin) was determined by iodometrically. The estimated

amount of un-reacted N-Chlorosaccharin, showed that one mole of NCSA consumes one mole of flavoxate. The 3-methyl-4-oxo-2-phenyl-4H chromene-8-(2-acetaldehyde) carboxylate found as the main end-product of oxidation which conformed by by paper chromatography[5] using light petroleum ether, chloroform and 1- butanol (2:2:1; v/v/v) as the solvent and iodine as the reducing agent. The observed Rf = 0.62 value is consistent with the given Rf value in the literature. The Piparidine also indentified as side-product by spot test[6].



RESULTS AND DISCUSSION

The oxidation of flavoxate with NCSA was kinetically investigated at several initial concentrations of the reactants in acid media. The salient feature obtained is discussed. Under pseudo-first-order conditions ([FX] >> [NCSA]) at solvent composition and temperature, plots of log (a-x) vs. time were linear ($r > 0.91$) indicating a first-order dependence of rate on [NCSA]. The pseudo-first-order rate constants (k_1) calculated is given in Table 1. Further, the values of k_1 calculated from these plots are unaltered with variation of [NCSA], confirming the first-order dependence on [NCSA]. The rate constant (k_1) have been found to increase with increase in the concentration of 2-phenylethylamine and plot of k_1 Vs [FX] was linear

with slope less than unity, indicating a fractional order dependence on rate of flavoxate (Fig.1,2, Table-1). Similarly, the reaction is fully acid catalyzed because, the rate of reaction increases with increase in [HCl] (fig.3, Table: 1).The effect of changing solvent composition on the reaction rate was studied by varying concentration of Ac.OH from 20-60 %. The rate constants suggest that the rate of reaction slightly decreases with increasing Ac.OH content of the solvent mixture. The plot of log k_1 Vs 1/D was found to be linear with negative slope indicating the involvement of two dipoles or an ion–dipole reaction (fig.4). Variation of saccharin one of the products of oxidation, had negative effect on the rate of reaction. The HCl catalyzed oxidation reaction of flavoxate with NCSA at different initial concentrations of acrylonitrile have been investigated. The reaction neither induces polymerization nor retards the reaction rate, which may be attributed to the inertness shown by free radicals.

Effect of temperature: The rate of oxidation was determined at different temperatures and the Arrhenius plots of log *k* vs. 1/T were all linear from this plot, the activation and thermodynamic Parameter for equilibrium step and rate determining step of the scheme was evaluated (**Table 2).**

Table- 1
Effect of variation of reactants on pseudo first-order rate constant k_1 at 313K.

10^2 [FX] (mol. dm.$^{-3}$)	10^3[NCSA] (mol. dm.$^{-3}$)	10^3 [H^+] (mol. dm.$^{-3}$)	% Ac.OH-H_2O (v/v)	$k_1 x 10^3$ (min^{-1})
1.25	1.00	1.25	30	1.30
1.25	1.25	1.25	30	1.29
1.25	2.00	1.25	30	1.28
1.25	2.50	1.25	30	1.29
1.25	4.00	1.25	30	1.31
1.25	5.00	1.25	30	1.24
1.00	2.50	1.25	30	1.03
1.25	2.50	1.25	30	1.29
2.00	2.50	1.25	30	1.69

2.50	2.50	1.25	30	1.91
4.00	2.50	1.25	30	2.31
5.00	2.50	1.25	30	2.40
1.25	2.50	1.00	30	0.87
1.25	2.50	1.25	30	1.29
1.25	2.50	2.00	30	2.25
1.25	2.50	2.50	30	2.88
1.25	2.50	4.00	30	4.83
1.25	2.50	5.00	30	5.75
1.25	2.50	1.25	20	0.87
1.25	2.50	1.25	30	1.18
1.25	2.50	1.25	40	1.29
1.25	2.50	1.25	50	1.42
1.25	2.50	1.25	60	1.67

Table- 2
THERMODYNAMIC PARAMETER

[NCSA] : $2.50X10^{-3}(mol.dm^{-3})$
[FX] : $1.25X10^{-2}(mol.dm^{-3})$
HOAc-H_2O : 30% (v/V) ;

Substrate	Ea (kJ mol^{-1})	A (s^{-1})	$\Delta H^{\#}$ (kJ mol^{-1})	$-\Delta G^{\#}$ (kJ mol^{-1})	$-\Delta S^{\#}$ JK mol^{-1}
Flavoxate	**42.03 ±0. 66**	**$2.36x10^{7}$ ±0.76**	**47.38 ±0.97**	**-88.68 ±0.58**	**-98.45 ±0. 57**

Reactive Species and Mechanism: It has been shown that probable reactive species of NCSA in acid solution are NCSA itself or Cl^{+} or NCSA viz., (HOCl) as active oxidizing species, and negative effect of the initially added product, saccharin restricts us to take HOCl as the oxidizing species. Based on the above discussions and observed kinetic data, a probable mechanism is proposed for the oxidation of FX.

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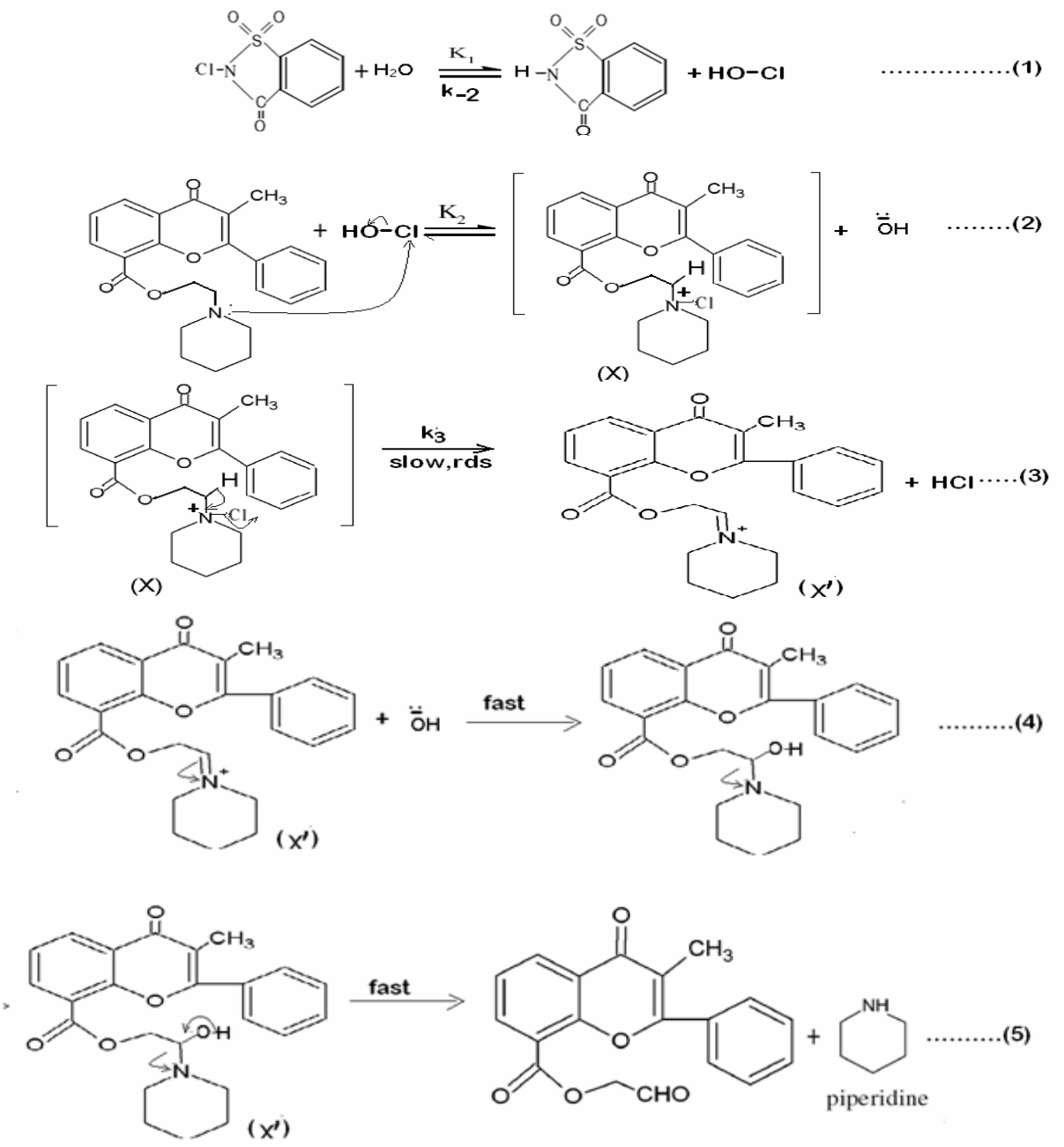
MECHANISTIC PATHS FOR THE OXIDATION FLAVOXATE-NCSA SYSTEM



The derived rate equation is:

$$k_{obs.} = \frac{K_1 K_2 k_3 [\mathbf{FX}]}{[\mathbf{Sac.}]\{\mathbf{k_{-2}} + \mathbf{k_3}\}} \quad \text{.....(9)}$$

The above rate equation is good agreement with the observed experimental data and results. Thus, mechanism is also in good agreement with the work reported by Singh[7, 8]

The observed $\Delta S^{\#}$ values are large and negative. It may be interpreted that the fraction of collisions become more stringent and decomposition of activation complex is a quite slow process. $\Delta H^{\#}$ indicates that the reactions are enthalpy controlled. Further, the constancy in the calculated values of $\Delta G^{\#}$ for this oxidation reaction indicates that the same type of the reaction mechanism could be operative for the reaction.

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