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Original Article

Kinetics and Mechanism of the Oxidation of Chloroquinephosphate with Chloramine-B in Acidic Buffer Medium

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ABSTRACT

The kinetics of oxidation of Chloroquine phosphate [CP] by Chloramine-B [Sodium N-chlorobenzene Sulfonamide, CAB] has been studied in acidic buffer solution of P^H 4 at 303 K. The reaction was first order with respect to [CAB], fractional order with respect to [H^+] and [CP]. Activation parameters were evaluated from the kinetic data at different temperatures. Negative entropy of activation indicated the involvement of a rigid complex in the activated state. The dependence of the reaction rate on dielectric constant of the medium, ionic strength, reaction product and solvent isotope effect were studied. The reduction product benzene sulphonamide [BSA] has no effect on the reaction rate. The reaction product was identified by spectral (IR and NMR) data. Rate equation is derived to account for the observed kinetic data and a probable mechanism has been proposed.

Keywords: Kinetics, Oxidation, Chloroquine Phosphate, Chloramine-B.

INTRODUCTION

The chemistry of chloramines has attracted the attention of many investigators on account of nature of the chemistry of N-haloamines, their ability to act as source of halonium cations, hypolite species and N- anions, which act both as bases and nucleophiles [1]. These compounds contain positive halogen and acts as chlorinating or oxidizing agents [2, 3]. They interact with a wide range of functional groups, affecting a variety of molecular transformation. A prominent member of this class is Chloramine-B (CAB, $C_6H_5SO_2NClNa.1.5H_2O$) is a stable compound and is found to be better oxidizing agent than its analogue CAT. However there is less information in the literature on CAB, particularly with respect to the oxidation kinetics of pharmaceuticals [4-11]. Preliminary experimental results revealed that the present oxidation reactions by CAB in acidic buffer medium were facile. Therefore, CAB has been chosen as an oxidant in the present investigation.
Chloroquine Phosphate [CP] [$C_{18}H_{26}N_3Cl.H_3PO_4$] [7-Chloro-4-(4-diethyl amino-1-methylbutyl amino) quinoline phosphate or N^4-(7-chloro-4-quinolinyl)-N^1-N^1-diethyl- 1, 4- pentane diamine Phosphate] is an effective antimalarial drug, anti-inflammatory, mild antipyretic and analgesic.

It is noted that inspite of the importance of this drug, relatively little is known about its mode of action at the molecular level, its kinetic and mechanistic pathway in red-ox system. So far no kinetics and mechanistic details are available on the oxidation of this drug. Accordingly, it is of immense interest to follow the oxidation kinetics of this drug with halogen^{+1} oxidant. The present paper reports the kinetics of oxidation of CP by CAB in acid buffer medium in view of investigating the mechanism of this drug in solution.

EXPERIMENTAL

Materials and Methods: The purity of Chloramine-B (Fluka, Switzerland) was checked iodometrically through its active chlorine content. An aqueous solution of the compound was prepared, standardized periodically by the iodometric method and preserved in brown bottles to prevent any photochemical deterioration. The substrate CP of analytical grade was used, solvent isotope studies were made by using D_2O [Barc,India]. Standard buffer solutions were used [12]. Doubly distilled water was used throughout the course of the reaction.

Kinetic Measurements: The kinetic runs were performed under pseudo-first order conditions with

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a large excess of substrate over oxidant at 303 K. The reaction was carried out in glass stoppered Pyrex boiling tubes with outer surface coated black to eliminate photochemical effects. Solution containing requisite amount of CAB, buffer solution(to keep total volume constant for all runs) were taken in the tube and thermostated at 303 K for thermal equilibrium.A measured amount of CP solution also thermostated at the same temperature and rapidly added to the mixture with stirring in the boiling tube. The mixture was periodically shaken to ensure uniform concentrations and the progress of the reaction was monitored by iodometric determination of unreacted CAB in a measured aliquot of the reaction mixture at different intervals of time. The course of the reaction was studied for more than two half lives. The pseudo- first order rate constants, calculated from linear plots of log [CAB] versus time, were reproducible within ±3%.

Stoichiometry: A known excess of oxidant was allowed to react with [5.00 $\times10^{-3}$mol dm^{-3}] CP for 24 hr under the experimental conditions. The results showed the consumption of two moles of oxidant and following stoichiometric equation was proposed.

$C_{18}H_{26}N_3Cl.H_3PO_4+2PhSO_2NClNa \rightarrow C_{14}H_{15}N_2O_2Cl.H_3PO_4+2PhSO_2NH_2+2NaCl+HN(C_2H_5)_2$

Product analysis: The presence of reduction product benzene sulfonamide (BSA) was identified by TLC [5] using a mixture of petroleum ether, chloroform and n- butanol (2:2:1 v/v) as the solvent with iodine as the detecting reagent (Rf = 0.88). The stoichiometric reaction was repeated and the BSA was extracted with a suitable solvent. The GC-MS (M^+ parent ion peak with mass at 157) confirm BSA. After elimination of BSA, the residual solution was introduced into a column containing respective ion exchange resin in order to remove Na^+ and Cl^- ions and diethyl amine was extracted with ether. The final eluate was concentrated to 30% and the amount obtained was stochiometric with the concentration of CP used for the reaction. Furthermore, the product was characterized by IR and NMR spectral studies. IR (KBr) $r_{max}cm^{-1}$: 1729 s (C=O) acid, 3059 s (NH) and 710 s (C-Cl). ^{1}H NMR (400 MHz, CDCl3, δppm) 8.36 (d, 1H, Ar), 8.23 (d, 1H, Ar), 6.44(d, 1H, Ar), 7.36-7.9(s, 2H, Ar), 3.4(s, 1H, NH), 11.43(s, 1H, COOH), 3.45(m, 1H, methyne), 2.30(t, 2H, methylene), 1.89(m, 2H, methylene), 1.53(m, 3H, methyl).

RESULTS

The oxidation of CP by CAB was carried out at 303 K in acidic buffer medium. Since the reaction was facile in acidic P^H medium, a detailed investigation on the kinetics of oxidation CP by CAB was made in acidic buffer medium. The kinetics of oxidation of CP in acidic buffer of P^H 4 containing [5.00 $\times10^{-3}$mol dm^{-3}] CP was investigated at several initial concentrations [1.00 $\times10^{-4}$-12.50 $\times10^{-3}$mol dm^{-3}] of CAB was studied at 303 K. Plots of log [CAB] versus time are linear indicating a first- order dependence of the rate on [oxidant](Table-I).

With different initial concentrations of CP [1.00 $\times10^{-3}$ – 12.50$\times10^{-3}$mol dm^{-3}] in acidic buffer containing [5.00 $\times10^{-4}$mol dm^{-3}] oxidant at 303K, plots of log k_{obs} versus [CP] were linear with a slope of 0.5 indicating fractional order dependence on [CP]. The reaction was carried out with [5.00$\times10^{-4}$mol dm^{-3}] oxidant and [5.00$\times10^{-3}$mol dm^{-3}] CP in the presence of various acidic buffer solutions [P^H 2- 5.2] at 303 K; the rate increased with increase in P^H (Table-II), plots of log k_{obs} versus P^H were linear with a slope of 0.45 indicating fractional order dependence of the rate on P^H of the medium. Addition of reduction product benzene sulfonamide had no effect on the rate, indicating that it is not involved in pre-equilibrium step before the rate-determining step. The rate constant for the oxidation of CP in D_2O medium at 303 K was determined. Variation of the ionic strength of the medium by adding $NaClO_4$ [1.00 $\times10^{-2}$ – 7.50$\times10^{-2}$mol dm^{-3}], affect the rate slightly with slope 0.058. The reaction of CAB [5.00 $\times10^{-4}$ mol dm^{-3}] and CP [5.00 $\times10^{-3}$mol dm^{-3}] was carried out in the mixtures of methanol and water of various compositions (% v/v) containing acidic buffer at 303 K. The reaction rate slightly decreased with increase in MeOH content (where D values were obtained from the literature [13, 14]) in the medium (Table-III). The effect of temperature on the rate was studied by performing the kinetic experiments at various temperatures (283-313 K) while keeping other experimental conditions constant. From the linear Arrhenius plot of log k^1 v/s 1/T, values of composite activation parameters, energy of activation (Ea), enthalpy of activation ($\Delta H^{\#}$), entropy of activation ($\Delta S^{\#}$), free energy of activation ($\Delta G^{\#}$) and logA are computed. These results are compiled in Table-IV.

DISCUSSION

Investigations of Higuchi et al [15], Bishop and Jennings [16] and Morris et al [17], on Sodium-N-haloarenesulfonamidates have shown that several equilibria exist in acidified Chloramine-T (CAT) solutions. The work of Zilberg[18],Mogilevski et al [19] and Mahadevappa et al[20] have indicated the

operation of similar equilibria in acidified CAB solution.

The chemistry of aqueous solution of Chloramine-B is very complex because in aqueous solutions CAB exhibit several equilibria as in the case of aqueous Chloramine-T solution. CAB ionizes in aqueous solution

$PhSO_2NClNa \rightleftharpoons PhSO_2NCl^- + Na^+$

The anion picks up a proton in acid solution to give monochloramine ($PhSO_2NHCl$), which undergoes disprotonation or hydrolysis to give dichloramine, benzene sulphonamide and HOCl.

$PhSO_2NCl^- + H^+ \rightleftharpoons PhSO_2NHCl$

$2\ PhSO_2NHCl \rightleftharpoons PhSO_2NCl_2 + PhSO_2NH_2$

$PhSO_2NHCl + H_2O \rightleftharpoons PhSO_2NH_2 + HOCl$

$PhSO_2NCl_2 + H_2O \rightleftharpoons PhSO_2NHCl + HOCl$

$HOCl + HCl \rightleftharpoons H_2 + Cl_2$

Hence, the probable oxidising species present in acidified CAB solutions are $PhSO_2NHCl$, $PhSO_2NCl_2$ and HOCl. If $PhSO_2NCl_2$ were the oxidising species, the rate law would predict a second order dependence on [CAB]. If HOCl were involved a first- order retardation of the rate by the reaction product ($PhSO_2NH_2$) would be expected. However, no such effects were noticed. Therefore, the effective oxidising species in the rate determining step could be conjugate acid ($PhSO_2NHCl$) in acid solution of CAB in the present system.

In the present investigation, oxidation of CP by CAB in acidic buffer medium shows fractional order dependence on [CP] and clearly indicated complex formation between the substrate and oxidant in an equilibrium step prior to the rate determining step.

Based on the above facts, the mechanism of the reaction could be explained by scheme I to account all the observed kinetic data.

$PhSO_2NCl^- + H^+ \overset{k_1}{\rightleftharpoons} PhSO_2NHCl$ (X) ….1 fast

$X + S \overset{k_2}{\rightleftharpoons} X^1$ …….2 fast

$X^1 \xrightarrow{k_3} X^{11}$ ……3 slow and rds

$X^{11} + PhSO_2NHCl \longrightarrow$ Products …4 fast

Scheme I

From the slow step 3 of scheme I

$$Rate = \frac{-d[CAB]_t}{dt}$$

Therefore Rate = $k_3 [X^1]$ 5

The total effective concentration of CAB is $[CAB]_t$, then

$[CAB]_t = [PhSO_2NCl^-] + [X] + [X^1]$ 6

From step 1 of scheme I

$k_1 = [X] / [PhSO_2NCl^-] [H^+]$ …..7

$[PhSO_2NCl^-] = [X] / k_1[H^+]$ ….8

From step 2 of scheme I

$k_2 = [X^1] / [X] [S]$ …..9

$[X] = [X^1] / k_2 [S]$ ……10

By substituting for [X] from equation 10 into equation 8 we get

$[PhSO_2NCl^-] = [X^1] / k_1k_2 [S] [H^+]$ ….11

By substituting for [X] and $[PhSO_2NCl^-]$ from equation 6 one obtains

$[CAB]_t = [X^1] / k_1 k_2 [S] [H^+] + [X^1] / k_2 [S] + [X^1]$ …12

$[CAB]_t = [X^1] + [X^1] k_1[H^+] + [X^1] k_1 k_2 [S] [H^+] / k_1 k_2 [S] [H^+]$ …13

$[CAB]_t = [X^1][1 + k_1[H^+] + k_1 k_2 [S] [H^+]] / k_1 k_2 [S] [H^+]$ …14

From which,

$[X^1] = k_1 k_2 [S] [H^+][CAB]_t / 1 + k_1[H^+] + k_1 k_2 [S] [H^+]$ ..15

By substituting $[X^1]$ the equation 5 becomes

Rate = $k_1\ k_2\ k_3\ [S]\ [H^+][CAB]_t\ /\ 1 + k_1[H^+]\ + k_1\ k_2\ [S]\ [H^+]$ …16

Rate law 16 is in accordance with the experimental results, where in a first order dependence of rate on $[CAB]_0$ and fractional orders on each $[substrate]_0$ and $[H^+]$ was noticed

Since rate= $k^1\ [CAB]_t$

k^1 = rate / $[CAB]_t$

equation 16 can be transformed as

$k^1 = k_1\ k_2\ k_3\ [S]\ [H^+]\ /\ 1 + k_1[H^+]\ + k_1\ k_2\ [S]\ [H^+]$ …17

$1/\ k^1 = 1 + k_1[H^+]\ + k_1\ k_2\ [S]\ [H^+]\ /\ k_1\ k_2\ k_3\ [S]\ [H^+]$ …18

$1/\ k^1 = 1\ /\ k_1\ k_2\ k_3\ [S]\ [H^+]\ + 1\ /\ k_2\ k_3\ [S]\ + 1\ /\ k_3$ …19

A detailed mechanism involving electron transfer during the oxidation of CP by CAB in acidic buffer medium is depicated in reaction scheme II. The protonated CAB (X) reacts with the substrate (S) to form the intermediate (X^1). Then intermediate X^1 undergoes deprotonation to give X^{11}. Further X^{11} undergoes reaction to give oxidation product.

CONCLUSION:

Oxidative cleavage of Chloroquine phosphate with CAB in acidic buffer medium at 303 K has been studied. The active species of CAB is found to be $PhSO_2NHCl$. The stoichiometry of the reaction was found to be 1:2 and the oxidation products were identified by spectral studies. An overall mechanism sequence is proposed and the rate law is derived. The proposed mechanism is in conformity with the observed kinetic data.

Table I: Effect of varying oxidant and substrate concentration on the reaction rate in acidic buffer medium at 303 K.

$[CP]\times10^3$ mol/dm^3	$[CAB]\times10^4$ mol/dm^3	$k^1\ \times10^3$ (s^{-1})
1.00	5.00	0.74
5.00	5.00	1.34
7.50	5.00	1.88
10.00	5.00	2.22
12.50	5.00	2.74
5.00	1.00	1.363
5.00	5.00	1.343
5.00	7.50	1.333
5.00	10.00	1.351
5.00	12.50	1.345

Table II: Effect of varying P^H of medium on the reaction rate at 303 K. [CAB] = 5.00×10^{-4}mol dm^{-3}; [CP] = 5.00×10^{-3}mol dm^{-3}.

P^H	$k^1\ \times10^3$ (s^{-1})
2.00	0.300
3.00	0.692
4.00	1.343
4.70	2.632
5.20	3.120

Table III: Effect of varying dielectric constant of medium on the reaction rate at 303 K.
[CAB] = 5.00×10^{-4}mol dm^{-3}; [CP] = 5.00×10^{-3}mol dm^{-3}.

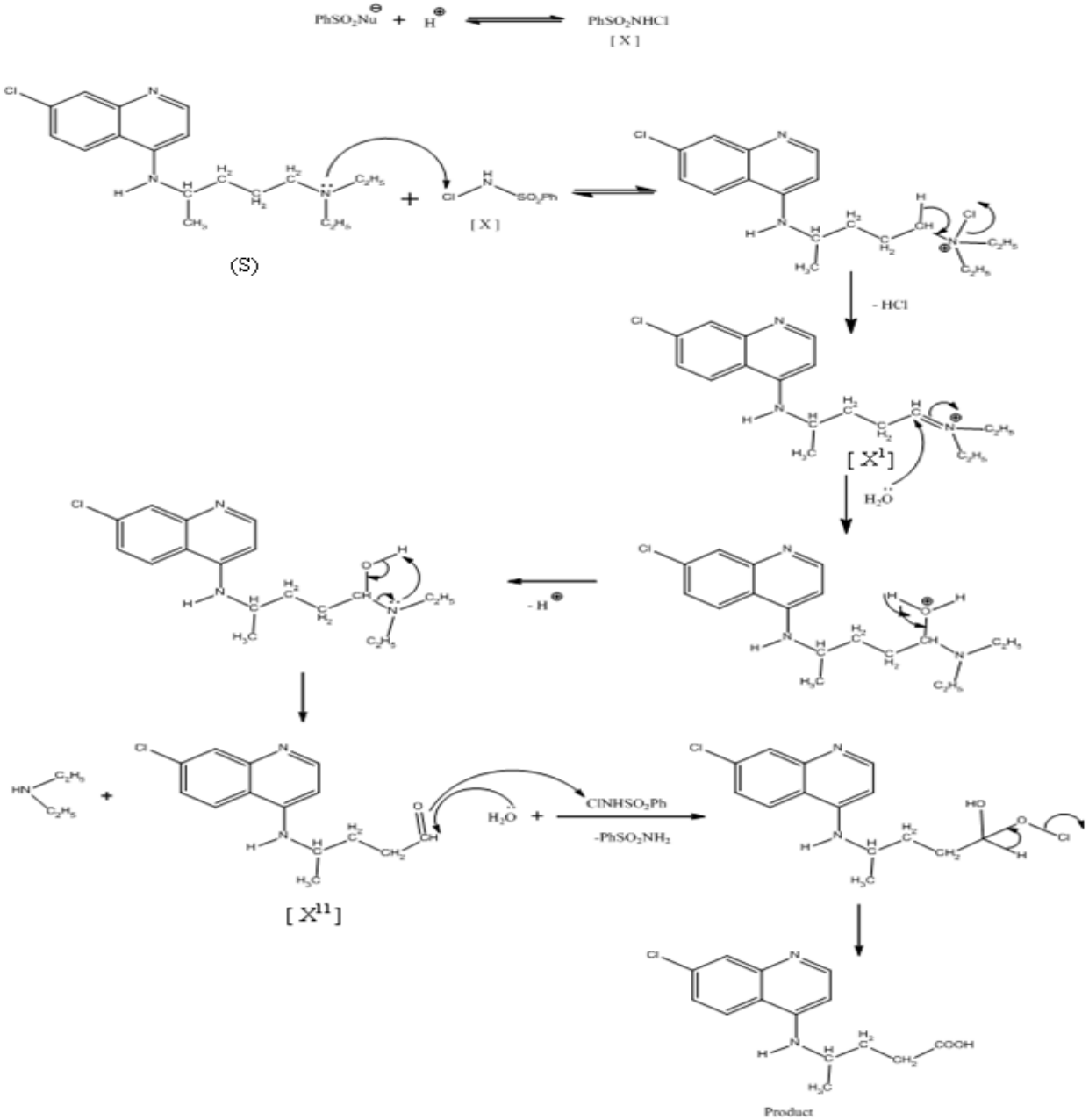
% MeOH	D	$k^1\ \times10^4$ (s^{-1})
5.00	74.55	6.90
10.0	72.37	6.39
15.0	70.19	6.28
20.0	67.48	6.02
25.0	65.32	5.98

Table IV: Effect of temperature on rate of reaction and activation parameters for the oxidation of CP by CAB in acid buffer medium.

[CAB] = 5.00 ×10^{-4}mol dm^{-3}; [CP] = 5.00 ×10^{-3}mol dm^{-3}.

Temperature in K	k^1 ×10^3 (s^{-1})	Activation parameters
283	0.712	Ea (KJ mol^{-1}) = 17.950
293	0.942	$\Delta H^{\#}$ (KJ mol^{-1}) = 15.471
303	1.343	$\Delta G^{\#}$ (KJ mol^{-1}) = 21.462
313	1.742	$\Delta S^{\#}$ (J K^{-1} mol^{-1}) = −72.032
323	1.989	Log A = 2.058

Mechanism:



Scheme II

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