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OXIDATION KINETICS AND MECHANISTIC INVESTIGATION OF QUININE SULPHATE BY CHLORAMINE-B IN ACIDIC CHLORIDE SOLUTION

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ABSTRACT: The kinetics of oxidation of quinine sulphate [8α, 9R-6[1]- methoxycinchonan- 9 - ol sulphate], (QS) by Chloramine-B (Sodium N-Chlorobenzene Sulphonamide, CAB) has been studied in aqueous hydrochloric acid medium at 303 K. The reaction rate shows a first order with respect to [CAB], fractional order with respect to [HCl] and [QS]. 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 dielectric constant of the medium has a small effect on the rate. Ionic strength and the reduction product benzene sulphonamide [BSA] do not affect the reaction rate. The solvent isotope effect is studied. The reaction products are identified and characterized by spectral (IR and NMR) data. The proposed reaction mechanism and the derived rate equation are consistent with the observed kinetic data.

INTRODUCTION: The chemistry of chloramines has attracted the attention of many investigators on account of nature of the chemistry of N-halo amines, their ability to act as a source of halonium cations, Hypolite species and N- anions, which act both as bases and nucleophiles [1]. These compounds contain positive halogen and are mild oxidants [2]. 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 a better oxidizing agent than its analog CAT.

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However there is less information in the literature on CAB, particularly concerning the oxidation kinetics of pharmaceuticals [3-12], Preliminary experimental results revealed that the present oxidation reactions by CAB in HCl medium were facile. Therefore, CAB has been chosen as an oxidant in the present investigation. Quinine sulfate $[(C_{20}H_{24}N_2O_2)_2.H_2SO_4.2H_2O]$ an alkaloid obtained from the bark of species of cinchona QS is an effective antimalarial drug, mild antipyretic and analgesic. It is noted that despite the importance of this drug, relatively little is known about its mode of action at the molecular level, and also its kinetic and mechanistic pathway of this drug in the 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 QS by CAB in the acid 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 QS of analytical grade was used, solvent isotope studies were made by using D_2O [Barc, India]. Doubly distilled water was used throughout the reaction.

Kinetic Measurements: The kinetic runs were performed under pseudo-first order conditions with a large excess of the 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. Appropriate amounts of the substrate, HCl solutions, and water (to keep the total volume constant for all runs) were taken in the tube and thermostated at 303 K for thermal equilibrium.

A measured amount of CAB solution also thermostated at the same temperature was 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 2-4%.

Stoichiometry: A known excess of oxidant was allowed to react with [5.00×10^{-3} mol dm^{-3}] QS in the presence of various concentrations [2.50×10^{-2} _10.0×10^{-2} mol dm^{-3}] of HCl at 303 K. The residual oxidant in each case was determined iodometrically after 24 h. The results showed the consumption of one mole of oxidant and following stoichiometric equation was proposed.

$C_{20}H_{26}N_2O_6S + PhSO_2NClNa \rightarrow C_{20}H_{24}N_2O_6S + PhSO_2NH_2 + Na^+ + Cl^-$

Quinine Sulphate CAB Quininone BSA:

Product Analysis: The presence of reduction product benzenesulfonamide (BSA) was identified by TLC [4] using a mixture of petroleum ether, chloroform and n- butanol (2:2:1 v/v) as the solvent with iodine as the detecting reagent (R_f = 0.88). The stoichiometric reaction was repeated, and the BSA was extracted with a suitable solvent. DCI mass spectra of the products were obtained on a 70 ev, Shimadzu SQP 5000 GC-MS spectrometer with class k 54 k software data processing system. The upper mass limit was 1100amu. The GC capillary column used was DB-1 (J and W scientific) with a programmed column temperature range of 80 – 250 °C. 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 cation ion exchange resin to remove Na^+ ions. The final eluate was concentrated to 30%, and the amount obtained was stoichiometric with the concentration of QS used for the reaction. Furthermore, the product was characterized as (8α,)- 6^1- methoxycinchonan- 9- one- sulfate (Quininone) using IR and NMR spectral studies.

IR (KBr) r_{max} cm^{-1}: 1735 cm^{-1} s (due to ketonic C=O stretch), H^1- NMR (DMSO), ppm/δ : 9.98(1H, s, NH), 8.7(1H, d, ArH), 7.95(1H, d, ArH), 7.3-7.7(3H, m, ArH), 5.75-5.9(1H, m, alkene H), 4.85-5.1(2H,d, alkene H), 3.9(3H, s, OMe), 2.56-2.8(2H, d, CH), 1.57-2.0(4H, m, CH_2), 1.4-1.57(4H, t, CH_2).

RESULTS: Oxidation of QS by CAB was carried out at 303 K in the presence of a known concentration of mineral acids. Since the reaction was facile in HCl medium, a detailed investigation on the kinetics of oxidation was made in HCl medium.

Kinetics of oxidation of QS [5.00×10^{-3} mol dm^{-3}] by the oxidant at constant concentration [1.00×10^{-1} mol dm^{-3}] of HCl was studied at various initial concentrations [2.50×10^{-4}-1.00×10^{-3} mol dm^{-3}] of CAB at 303 K. Plots of log [CAB] versus time are linear indicating a first-order dependence of the rate on [oxidant] **Table 1**. With different initial concentrations of QS [1.00×10^{-3} – 10.00×10^{-3} mol dm^{-3}] in [1.00×10^{-3} mol dm^{-3}] HCl containing [5.00×10^{-4} mol dm^{-3}] oxidant, plots of log k_{obs}

versus [QS] were linear with a slope of 0.46 indicating fractional order dependence on [QS].

The reaction was carried out with [5.00 × 10^{-4} mol dm^{-3}] oxidant and [5.00 × 10^{-3} mol dm^{-3}] QS in the presence of various concentrations [2.50 × 10^{-2} _10.0 × 10^{-2} mol dm^{-3}] of HCl at 303 K; the reaction was of fractional order (0.61) concerning [HCl]. To determine the order of the reaction concerning each of the [H^+] and [Cl^-], the reaction was also studied by varying the concentration of one ion while keeping the concentration of the other ion constant. The reaction was fractional order concerning each of the ions (0.43 to H^+ ions and 0.25 to Cl^- ions).

Addition of reduction product benzene sulfonamide did not affect the rate of oxidation. The rate constant for the oxidation of QS in D_2O medium at 303 K was determined. The reaction of CAB [5.00 ×10^{-4} mol dm^{-3}] and QS [5.00 × 10^{-3} mol dm^{-3}] was carried out in the mixtures of methanol and water of various compositions (% v/v) containing HCl [1.00 ×10^{-1} mol dm^{-3}] at 303 K. The reaction rate slightly increased with increase in MeOH content (where D values were obtained from the literature [13]) in the medium **Table 2**.

TABLE 1: EFFECT OF VARYING OXIDANT, SUBSTRATE, AND HCl CONCENTRATION ON THE REACTION RATE AT 303 K

[QS]×10^3 mol/dm^3	[CAB]×10^4 mol/dm^3	HCl×10 mol/dm^3	$k^{'}$ ×10^4 (s^{-1})
5.00	2.50	1.00	5.68
5.00	5.00	1.00	5.66
5.00	7.50	1.00	5.70
5.00	10.00	1.00	5.64
1.00	5.00	1.00	9.04
2.50	5.00	1.00	7.83
5.00	5.00	1.00	5.66
7.50	5.00	1.00	4.72
5.00	5.00	0.25	6.23
5.00	5.00	0.50	6.03
5.00	5.00	0.75	5.78
5.00	5.00	1.00	5.66

TABLE 2: EFFECT OF VARYING DIELECTRIC CONS-TANT OF MEDIUM ON THE REACTION RATE AT 303 K

% MeOH	D	$k^{'}$ ×10^3 (s^{-1})
5.00	74.55	1.079
10.0	72.37	1.179
15.0	70.19	1.201
20.0	67.48	1.351

[CAB] = 5.00 ×10^{-4} MOL dm^{-3}; [QS] = 5.00 ×10^{-3} MOL dm^{-3}; [HCL] =1.00 ×10^{-1} MOL dm^{-3}

The reaction rates were studied at different temperature (283-313 K). From the linear Arrhenius plot of log k^1 *v/s* 1/T, values of composite activation parameters, the energy of activation (Ea), enthalpy of activation ($\Delta H^{\neq}$), the entropy of activation ($\Delta S^{\neq}$), the free energy of activation ($\Delta G^{\neq}$) and logA are computed. These results are compiled in **Table 3**.

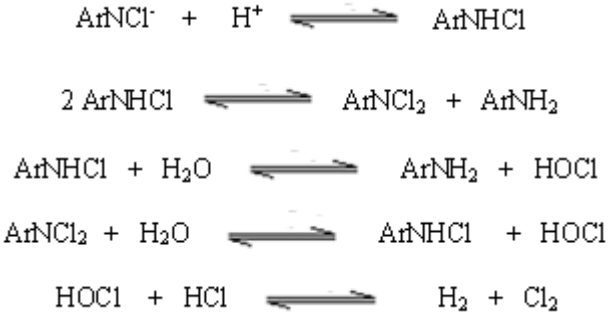
TABLE 3: EFFECT OF TEMPERATURE ON RATE OF REACTION AND ACTIVATION PARAMETERS FOR THE OXIDATION OF QS BY CAB IN ACID MEDIUM

Temperature in K	$k^{'}$ ×10^4 (s^{-1})	Activation parameters
283	2.148	Ea (KJ mol^{-1}) = 17.24
293	3.905	$\Delta H^{\neq}$ (KJ mol^{-1}) = 14.79
303	5.667	$\Delta G^{\neq}$ (KJ mol^{-1}) = 45.90
313	18.265	$\Delta S^{\neq}$ (J K^{-1} mol^{-1}) = −36.86
		log A = 2.04

[CAB] = 5.00 ×10^{-4} mol dm^{-3}; [QS] = 5.00 ×10^{-3} mol dm^{-3}; [HCl] =1.00 ×10^{-1} mol dm^{-3}

DISCUSSION: Investigations of Pryde and Soper, Higuchi et al., Bishop and Jennings and Hardy and Johnston, Morris [2], on Sodium-N-haloarenes sulfonamides have shown that similar equilibria exist in acid and alkaline solutions. 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 (ArNClNa, Ar=$C_6H_5SO_2$) ionizes in aqueous solution

The anion picks up a proton in acid solution to give monochloramine (ArNHCl), which undergoes disprotonation or hydrolysis



Thus, the probable oxidizing species present in acidified CAB solutions are ArNHCl, $ArNCl_2$, HOCl, and Cl_2. If $ArNCl_2$ were the oxidizing 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 ($ArNH_2$) would be expected. However, no such effects were noticed. Therefore, ArNHCl is the effective oxidizing species in the present system. In slightly acidic solution, ArNHCl undergoes protonation & forms an intimate ion pair with chloride ion.

Based on these facts, the mechanism of the reaction could be explained by **Scheme I,** which predicts simultaneous catalysis by H^+ & Cl^- ions.

$$PhSO_2NHCl + H^+ + Cl^- \underset{}{\overset{k_1}{\rightleftharpoons}} PhSO_2N^+H_2Cl.....Cl^- \quad (X) \qquad \text{..... 1 (fast)}$$

$$X + QS \underset{}{\overset{k_2}{\rightleftharpoons}} X^1 \qquad \text{..... 2}$$

$$X^1 \xrightarrow{k_3} X^{11} \qquad \text{.....3 (slow)}$$

$$X^{11} \longrightarrow \text{Product}$$

SCHEME 1

The overall rate is given by the slow step in **Scheme I,**

$$\text{Rate} = \frac{-d[CAB]_t}{dt} \qquad \text{.....4}$$

$$\text{Therefore} \quad \text{Rate} = k_3[X^1] \qquad \text{.....5}$$

If $[CAB]_t$ represents the total effective concentration of CAB, then

$$[CAB]_t = [PhSO_2NHCl] + [X] + [X^1] \qquad \text{.....6}$$

$$[PhSO_2NHCl] = \frac{[PhSO_2N^+H_2Cl.....Cl^-]}{k_1[H^+][Cl^-]} \qquad \text{.....7}$$

$$[CAB]_t = \frac{[X][1 + k_1[H^+][Cl^-]] + k_1[H^+][Cl^-][X^1]}{k_1[H^+][Cl^-]}$$

$$[X^1] = \frac{k_2[QS]\,k_1[H^+][Cl^-][CAB]_t}{[1 + k_1[H^+][Cl^-]]} \qquad \text{..... 8}$$

Therefore

$$\text{Rate} = \frac{k_3\,k_2k_1[QS][H^+][Cl^-][CAB]_t}{[1 + k_1[H^+][Cl^-]]}$$

$$K^1 = \frac{k_3\,k_2k_1[QS][H^+][Cl^-]}{[1 + k_1[H^+][Cl^-]]}$$

$$\frac{1}{K^1} = \frac{[1 + k_1[H^+][Cl^-]]}{k_3\,k_2k_1[QS][H^+][Cl^-]} \qquad \text{.....9}$$

This equation on rearrangement gives,

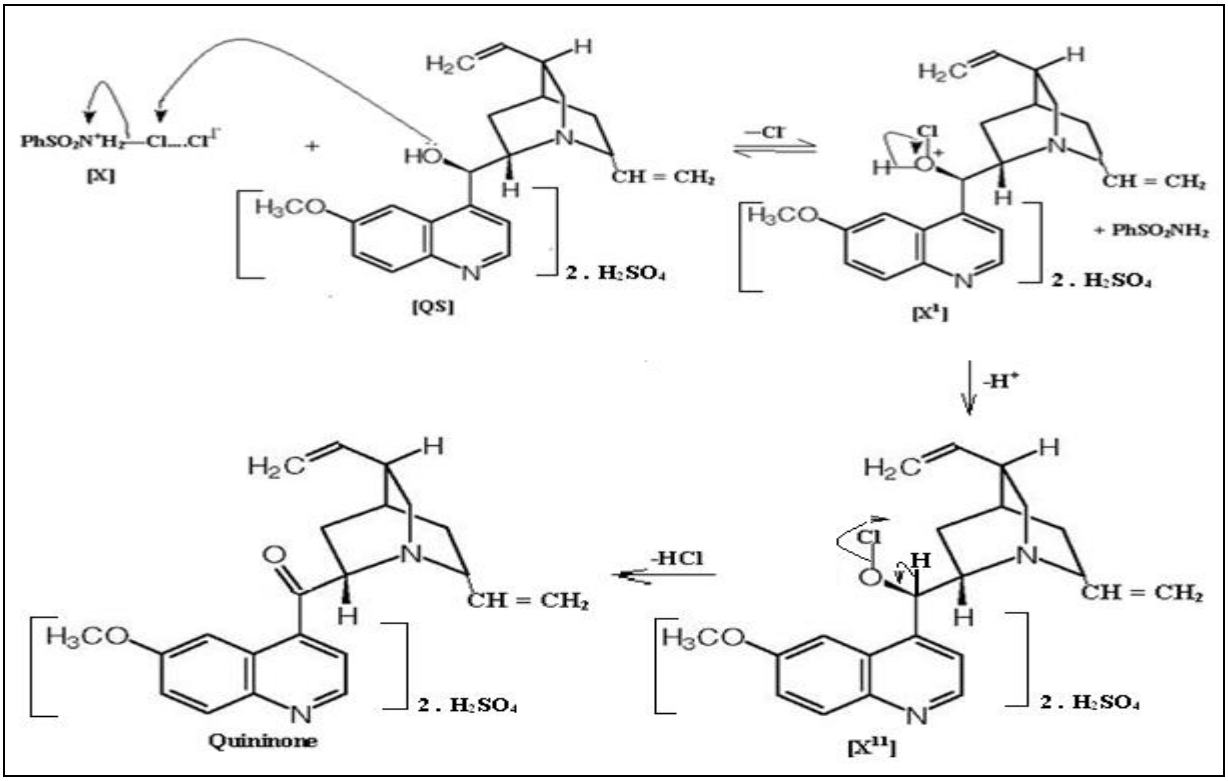
$$\frac{1}{K^1} = \frac{1}{k_3\,k_2k_1[QS][H^+][Cl^-]} + \frac{1}{k_3\,k_2[QS]}$$

Electron flow during the oxidation of QS by CAB is depicted in reaction scheme II. The protonated CAB (X) reacts with the substrate (QS) to form the intermediate (X^1). Then intermediate X^1 undergoes deprotonation to give X^{11}. Further X^{11} decomposes to give oxidation product.

CONCLUSION: Oxidative cleavage of Quinine Sulfate with CAB in the aqueous hydrochloric acid medium at 303 K has been studied. The active species of CAB is found to be ArNHCl. The stoichiometry of the reaction was found to be 1:1 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.

Mechanism:

$$PhSO_2NHCl + H^+ + Cl^- \underset{}{\overset{k_1}{\rightleftharpoons}} PhSO_2N^+H_2Cl.....Cl^- \quad (X)$$



SCHEME II

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CONFLICT OF INTEREST: Nil

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