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Mechanistic investigation on the oxidation of sulfaquinoxaline by chloramine-B: A Kinetic Approach

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ABSTRACT

Kinetics and mechanism of Sulfaquinoxaline [2-(p-aminobenzene) sulfonamide quinoxaline],(SQL) by Chloramine-B (CAB) in alkaline buffer solution of pH 9.2 over the temperature range of 293-323K has been studied. The reaction is first order with respect to [CAB] and fractional order with respect to each [SQL] and [OH^-]. The dependence of reaction rate on dielectric constant of the medium and ionic strength is consistent with the proposed mechanism. The observed retardation of rate by addition of reaction product, benzenesulfonamide indicated the involvement of OCl^- as the oxidizing species. Activation parameters are evaluated. Rate equation is derived to account for the observed kinetic data and the proposed reaction mechanism. The oxidation products are identified and characterized by spectral data.

Keywords: oxidation, sulfaquinoxaline, kinetics, mechanism, chloramine-B

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INTRODUCTION

Sulfaquinoxaline is an antiprotozoal, antimalarial drug widely used in the veterinary medicine [1-6]. Sulfanilamide and its derivatives have great antibacterial powers. They are used in medicine against "cocci infections-streptococci, gonococci and pneumococci". They compete with p-aminobenzoic acid in the enzymatic synthesis of dihydrofolic acid. This leads to a decreased availability of reduced folates that are essential in the synthesis of nucleic acids. After reviewing the literature, found that there was no information available on the oxidation kinetics of SQL with any oxidant. There was a need for understanding the oxidation mechanism of this medicinal compound, particularly with respect to veterinary drug. Hence, the present kinetic study gives an impetus, as the substrate SQL is a potent drug. Organic N-haloamines are mild oxidants containing a strongly polarized N-linked halogen in its +1 oxidation state. The prominent compound of this group is chloramine-T and the mechanistic aspects of many of its reactions have been documented [7,8]. The benzene analogue chloramine-B (Sodium N-chlorobenzenesulfonamide) is being important and received considerable attention as an oxidizing reagent [9,10]. However, a little information exists in the literature on CAB reactions [11,12] particularly with respect to the oxidation kinetics of pharmaceutical compounds, which may throw some light on the mechanism of metabolic conversions in biological systems.

In view of the available information and of continued interest on mechanistic studies of haloaminometric reactions in general and medicinal compounds in particular, the present studies are undertaken. The present paper reports for the first time the detailed kinetics of SQL oxidation by CAB in alkaline medium at 323K in order to (i) elucidate the reaction mechanism (ii) put forward an appropriate rate law (iii) identify the reactive species (iv) find the stoichiometry and (v) identify the oxidation products.

MATERIALS AND METHODS

Experimental

Chloramine-B (fluka) was purified by the method of verger and perlin [13]. Further, its purity was checked by iodometry for its active chlorine content and also by IR, NMR spectra. An aqueous solution of CAB was standardized iodometrically and stored in brown bottles to prevent photochemical deterioration. SQL (plama) was used without further purification. Aqueous solution of SQL was freshly prepared. All other chemicals used were of AR grade. Doubly distilled water was used throughout.

Kinetic Measurements

Experiments were carried out under pseudo-first order conditions by keeping $[SQL]_0 >> [CAB]_0$. The reaction was carried out in glass-stoppered pyrex boiling tubes whose outer surface was coated black to eliminate photochemical effects. Solutions containing requisite amounts of CAB, buffer solution and water (for constant volume) were taken in the tube and thermostated at 323K for thermal equilibrium. A measured amount of the SQL solution thermostated at the same temperature was rapidly added to the mixture and stirred well. The progress of the

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reaction was monitored up to two and half-lives by iodometric determination of unreacted CAB in 5ml aliquots of the reaction mixture withdrawn at different time intervals. The pseudo first-order rate constants (k'), calculated from the linear plots of log [CAB] vs. time were reproducible within ±3%.

Reaction Stoichiometry

The reaction mixture with varying ratios of CAB to SQL was equilibrated at 323K in alkaline buffer medium pH 9.2 for 48h. Iodometric titrations for unreacted CAB showed that 1 mole of SQL consumed 2 moles of oxidant confirming the following stoichiometry:

$2RNClNa + C_{14}H_{12}N_4SO_2 + 3H_2O \rightarrow 2RNH_2 + C_8H_7N_3O + C_6H_7SNO_4 + 2NaCl$

(where $R=C_6H_5SO_2$)

Product Analysis

The reactions were allowed to progress under stirred conditions for 48h at 323K. After completion of the reaction, the products were neutralized with HCl and extracted with ether. The combined ether extract was evaporated and subjected to column chromatography on silica gel (60-200 mesh) using gradient elusions (from dichloromethane to chloroform). After initial separation, the products were further purified by recrystallization. The organic products were subjected to spot tests [14] and again chromatographic analysis using TLC, which revealed the formation of oxidation products as N-hydroxyl amino benzene-4-sulfonic acid and N-hydroxyl-2-aminoquinoxaline. Further, these products were confirmed by IR and mass spectral analysis.

IR spectrum was recorded on Nicolet model impact 400D FT-IR spectrum (KBr pellets). IR spectral bands of N-hydroxyl amino benzene-4-sulfonic acid were observed at 3431cm^{-1} (-OH) and 3064cm^{-1} (-NH); N-hydroxyl-2-aminoquinoxaline at 3460cm^{-1} (-OH) and 3260 cm^{-1}(-NH). GC-MS was obtained on a 17A Shimadzu gas chromatograph with a QP-5050A Shimadzu mass spectrometer. The mass spectrum was obtained using the electron impact ionization technique. The mass spectrum showed a molecular ion peaks at 189 and 160 amu, clearly confirming N-hydroxyl amino benzene-4-sulfonic acid and N-hydroxyl-2-aminoquinoxaline respectively. All other peaks observed in MS can be interpreted in accordance with the observed structure.

The reduction product of CAB, benzenesulfonamide (BSA) was detected by paper chromatography [15]. Benzyl alcohol saturated with water was used as the solvent with 0.5% vanillin in 1% HCl solution in ethanol as spray reagent (R_f = 0.88). It was further confirmed by its melting point 149-150^{0}C (lim.m.p. =150-152^{0}C). It was also noticed that there was no further oxidation of these products under present kinetic conditions.

RESULTS

The oxidation of SQL by CAB was kinetically investigated at different initial concentrations of reactants in alkaline buffer medium at 323K.

Reaction kinetics

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Effect of Reactants on the Rate of Reaction

Table 1 Effect of varying concentrations of reactants on the rate of reaction at 323K in (pH = 9.2)

10^4 [CAB]$_0$ / M	10^3 [SQL] / M	10^4 k (s^{-1})
0.5	5.0	1.40
0.75	5.0	1.46
1.0	5.0	1.48
2.5	5.0	1.41
5.0	5.0	1.44
5.0	7.5	2.07
5.0	10.0	2.69
5.0	25.0	5.62
5.0	50.0	10.23

With the substrate in excess, at constant [SQL], pH and temperature, the [CAB]$_0$ was varied. Plots of log [CAB] vs. time were linear, indicating a first-order dependence of the rate on [CAB]$_0$. The values of pseudo first-order rate constant (k') are given in Table 1. Furthermore, the rate constant did not change with the change in [CAB]$_0$ confirming the first-order dependence on [CAB]$_0$. Under the similar experimental conditions, an increase in [SQL]$_0$ increased the k' values (Table 1). Plots of log k' vs. log [SQL]$_0$ was linear with a slope of 0.83 indicating a fractional order dependence on [SQL]$_0$. Furthermore, a plot of k' vs. [SQL]$_0$ was linear with a Y-intercept confirming the fractional order dependence on [SQL]$_0$.

Effect of pH on the Rate

Table 2 Effect of varying pH on the rate of the reaction at 323K

pH	10^4 k' (s^{-1})
8.1	0.6
9.2	1.44
10.3	3.64
11.2	7.07

[CAB] = 5.0 x 10^{-4} M, [SQL] = 5.0 x 10^{-3} M

The rate increases with increase in pH of the medium (Table 2). Plots of log k' vs. pH are linear with fractional slope (0.33), indicating a fractional-order dependence of the rate on [OH^-] of the medium.

Effect of Benzenesulfonamide on the Rate

Table 3 Effect of concentration of BSA on the rate of reaction at 323K

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10^3[BSA] / M	10^4 k'(s-1)
0.0	1.44
1.0	1.20
2.0	1.05
3.0	0.97
4.0	0.89
5.0	0.85

[CAB] = 5.0 x 10^{-4} M, [SQL] = 5.0 x 10^{-3} M and pH = 9.2

Addition of the reaction product, benzenesulfonamide (RNH_2), to the reaction mixture retards the rate (Table 3). Furthermore, plots of log k' vs. log [RNH_2] are linear with negative fractional slope (-0.20) indicating a negative fractional-order dependence of the rate on [RNH_2]. It also indicates that RNH_2 is involved in a fast pre-equilibrium to the rate-determining step.

Effect of the Ionic strength and Halide Ions on the Rate

Variation of the ionic strength (I) of the medium by adding $NaClO_4$ (0.01 - 0.05 mol dm^{-3}) has no effect on the rate. Also, addition of Cl^- ions in the form of NaCl (1.0 x 10^{-3} – 5.0 x 10^{-3} mol dm^{-3}) has negligible effect on the rate.

Effect of varying Dielectric Constant on the Rate

Table 4 Effect of varying dielectric constant (D) of medium on the rate of reaction at 323K

% MeOH (v/v)	D	10^2 / D	10^4 k' (s^{-1})
0	76.73	1.30	1.44
5	74.50	1.34	1.20
10	72.37	1.38	1.09
20	67.48	1.48	0.85
30	62.71	1.60	0.63

[CAB] = 5.0 x 10^{-4} M, [SQL] = 5.0 x 10^{-3}M, pH = 9.2

The dielectric constant (D) of the medium was varied by adding MeOH (0-30% v/v) to the reaction mixture. A decrease in the rate was noticed with decreasing in the rate was noticed with decreasing D (Table 4). Plot of log k' vs. 10^2/D was linear with negative slope supporting a rate determining step with a charge dispersal (where D values were obtained from the literature [16]), control experiments with MeOH indicated that its oxidation by CAB was negligible (< 2%) under the experimental conditions.

Effect of Temperature on the Rate

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Table 5 Effect of temperature on the rate of reaction and the values of activation parameters in alkaline buffer medium (pH = 9.2)

Temperature (K)	10^4 k' (S^{-1})	Activation parameters
293	0.21	E_a(kJ mol^{-1}) 55.20
303	0.40	$\Delta H^{\neq}$ (kJ mol^{-1}) 52.63
313	0.92	$\Delta G^{\neq}$ (kJ mol^{-1}) 77.13
323	1.44	$\Delta S^{\neq}$ (Jk^{-1} mol^{-1}) -79.50
		Log A 8.61

[CAB] = 5.0 x 10^{-4} M, [SQL] = 5.0 x 10^{-3} M

The effect of temperature on the rate was studied by performing the kinetic experiments at various temperatures (293-323K), while keeping other experimental conditions constant. From the linear Arrhenius plot of log k' vs. 1/T, activation energy and other thermodynamic parameters are given in Table 5.

Solvent Isotope studies

Studies of the reaction rate in D_2O medium for SQL revealed that solvent isotope effect $k'_{(H2O)} / k'_{(D2O)} \approx 0.89$.

Test for Free Radicals

Addition of the reaction mixture to the acrylamide monomer did not initiate polymerization indicating the absence of any free radicals produced during the course of reaction.

DISCUSSION

Investigations of Pryde and Soper [17], Higuchi et al [18], Bishop and Jennings [19] and Hardy and Johnston [20], Morris [21] et al, on Sodium-N-haloarenesulfonamidates have shown that similar equilibria exist in acid and alkaline solutions. The possible equilibria in aqueous Chloramine-B solution are:

$PhSO_2NClNa \rightleftharpoons PhSO_2NCl^- + Na^+$
$PhSO_2NCl^- + H^+ \rightleftharpoons PhSO_2NHCl$
$2PhSO_2NHCl \rightleftharpoons PhSO_2NH_2 + PhSO_2NCl_2$
$PhSO_2NCl_2 + H_2O \rightleftharpoons PhSO_2NHCl + HOCl$
$PhSO_2NHCl + H_2O \rightleftharpoons PhSO_2NH_2 + HOCl$
$OCl \rightleftharpoons H^+ + OCl^-$.

Therefore the possible oxidizing species in acid medium are $PhSO_2NHCl$, $PhSO_2NCl_2$, HOCl and probably $H_2OCl^{+\cdot}$ In alkaline solutions are $PhSO_2NHCl$, HOCl, $PHSO_2NCl^-$ and OCl^-. The

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oxidation potential of haloamine-sulfonamide system is pH dependent and decreases with increase in pH of the medium [22]. A retarding influence of OH^- ions on the reaction rate noticed in several haloaminometric reactions [23, 24] has been attributed for the formation of the conjugate acid RNHCl from $RNCl^-$ in a base retarding step.

$$PhSO_2NCl^- + H_2O \rightleftharpoons PhSO_2NHCl + OH^-$$

On increasing the concentration of NaOH, $PhSO_2NHCl$ gives NaOCl. Based on the preceding discussion and the observed kinetic results, a mechanism (scheme 1) is proposed for the oxidation of SQL by CAB in alkaline medium.

$$PhSO_2NHCl + NaOH \overset{K_1}{\rightleftharpoons} RNH_2 + NaOCl \quad \text{--- fast}$$

$$NaOCl + SQL \xrightarrow{k_2} X \quad \text{--- fast}$$

$$X \xrightarrow{k_3} X' \quad \text{--- slow and rds}$$

$$X' + NaOCl \xrightarrow{k_4} \text{Products} \quad \text{--- fast}$$

Scheme 1

The total effective concentration of oxidant, [CAB] is $[CAB]_t$, then
$[CAB]_t = [PhSO_2NHCl] + [NaOCl] + [X]$

That leads to the following rate law:

$$\text{Rate} = \frac{-d[CAB]}{dt} = \frac{K_1k_2k_3[CAB]_t[SQL][OH^-]}{[RNH_2] + K_1[OH^-]\{1+k_2[SQL]\}} \quad (1)$$

The rate law is in accordance with the observed kinetic date. Since rate = k' [CAB]t, eq. (1) can be transformed into eqs. (2) and (3):

$$\frac{1}{k'} = \frac{[RNH_2]}{k_3K_1k_2[SQL][OH^-]} + \frac{1}{k_3k_2[SQL]} + \frac{1}{k_3} \quad (2)$$

$$\frac{1}{k'} = \frac{1}{k_3k_2[SQL]}\left\{\frac{[RNH_2] + 1}{K_1[OH^-]}\right\} + \frac{1}{k_3} \quad (3)$$

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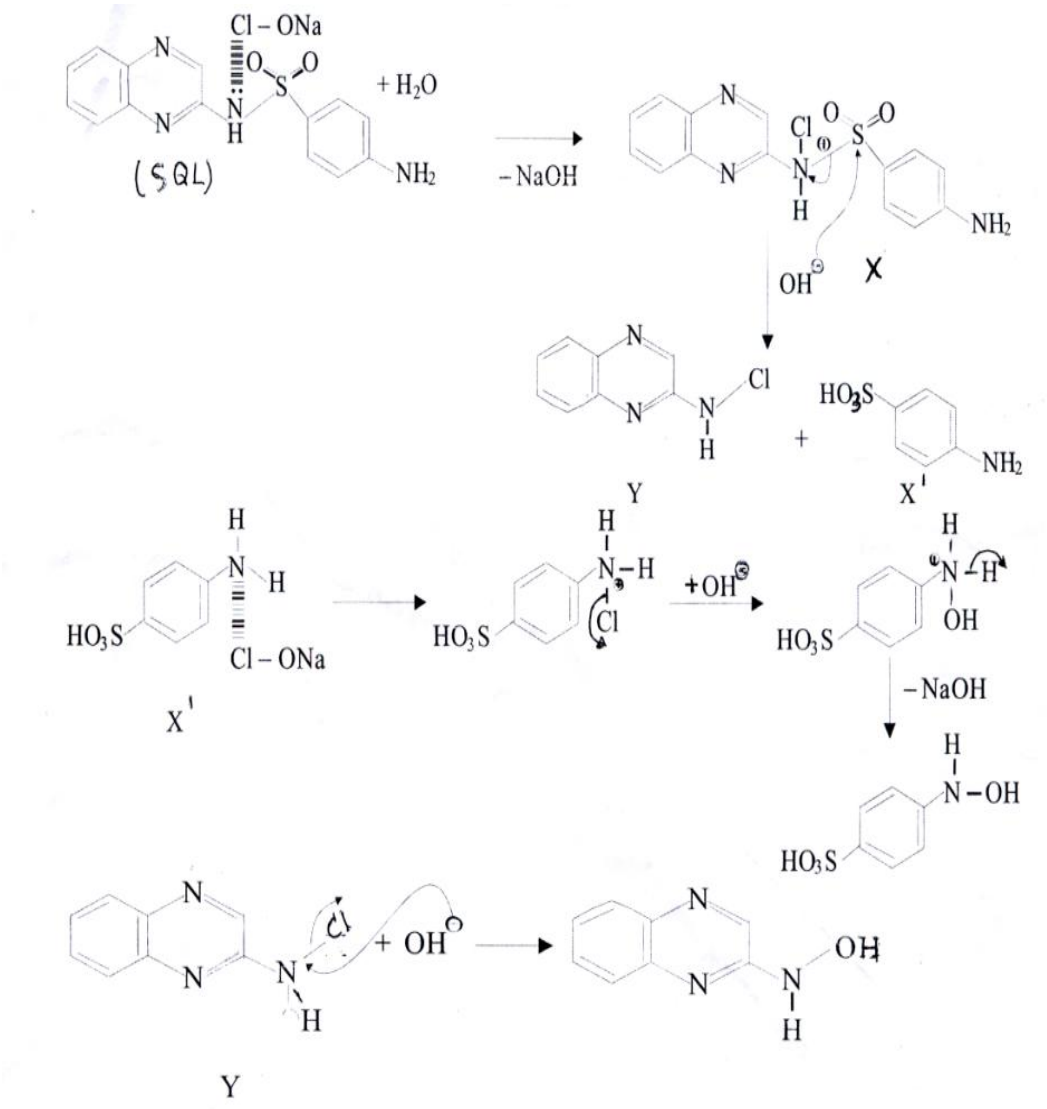
Based on rate law (3), plots of 1/k' vs. 1/ [SQL] and 1/k' vs. $[RNH_2]_0$, were found to be linear and from the slopes and intercepts of which the values of formation constants K_1, k_2 and decomposition constant k_3 were calculated. The near constant values of K_1, k_2 and k_3 support the proposed mechanism. Since a fractional order was noticed in [SQL], Michaelis-Menten kinetics [25] were adopted and [SQL] was varied at different temperature (293-323K). From the linear plots of 1/k' vs. 1/ [SQL] at each temperature, value of decomposition constant k_3 found to be $1.66 \times 10^{-3} s^{-1}$.



Scheme - 2

The change in the ionic strength of the medium does not alter the reaction rate, indicating that one of the interacting species involved in the rate-limiting step is nonionic in nature while the other is ionic. For a limiting case of zero angle of approach between two dipoles or an ion-dipole system, Amis [26] has shown that a plot of log k' vs. $10^2/D$ is linear with

a negative slope for a reaction between anion and a dipole or between two dipoles and positive slope for a cation-dipole interaction. The negative dielectric effect observed in the present studies (Table 4) clearly supports the anion-dipole interaction as shown in the proposed scheme. Solvent isotope studies show that $k'_{(H_2O)} / k'_{(D_2O)} < 1$. This is generally correlated with the fact that OD^- is a stronger base than OH^- and the present base catalyzed reactions, increase in the rate in D_2O medium is expected. The magnitude, however, is small compared to the expected value of 2 to 3 times greater, which can be attributed to the fractional order dependence on $[OH^-]$. These observations are also in confirmity with the proposed mechanism, which shows the decomposition of a complex species, X in the slow step.

A detailed mechanism involving electron transfer during the oxidation of SQL by CAB in alkaline buffer medium is shown in scheme 2. The species NaOCl reacts with the SQL forming an intermediate complex X which decompose to intermediate species X' and Y. The intermediate species Y further reacts with OH^- to form N-hydroxyl amino-2-quinoxaline. The intermediate X' so formed then reacts with another molecule of NaOCl to give the ultimate product N-hydroxyl amino benzene-4-sulfonic acid.

Moderate values of the E_a, $\Delta H^{\neq}$ and $\Delta G^{\neq}$, log A indicate that the transition state is highly solvated and support the reaction mechanism. The negative values of $\Delta S\neq$ indicate the involvement of compact transition state in which several degrees of freedom are lost during the reaction.

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