

Kinetics of Oxidation of Diazepam by N Bromosuccinimide in Acid Medium: A Mechanistic Study

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Authors' contributions

This work results from the collaboration between all authors. Author NN conceived, designed, and managed the study. Authors SM and PK performed the literature search, laboratory experiments and data analysis, and wrote the first draft of the manuscript. Author NMMG revised the manuscript and communicated it to the journal. All authors read and approved the final manuscript.

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ABSTRACT

The oxidation of diazepam (DZ) by N-Bromosuccinimide (NBS) in aqueous acid medium follows a first-order kinetics in [NBS] and a fractional-order each on [HCl] and [DZ]. The reaction stoichiometry involves one mol NBS consumed by one mol DZ. The rate of the reaction increases with the decrease in dielectric constant of the medium. Added products and the variation of ionic strength have no significant effect on the rate of the reaction. The oxidation products were identified by spectral analysis. A mechanism

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involving the formation of an intermediate NBS-DZ complex has been proposed. The solvent effect is consistent with the charge dispersion going into the transition state. The activation parameters for the reaction have been determined. The negative entropy of activation suggests the formation of a rigid, associative transition state involving loss of degrees of freedom.

Keywords: *Diazepam; N-bromosuccinimide; acid medium; oxidation kinetics; mechanism.*

1. INTRODUCTION

N-Bromosuccinimide (NBS) is a highly selective and relatively stable compound capable of oxidizing a number of organic and inorganic substrates [1-2]. It is a member of the class of N-halosuccinimide, which is an excellent source of positive halogen owing to its highly labile N-X bond [3]. It finds wide applications in promoting various halogenation and oxidation reactions.

Diazepam or 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, a psychotherapeutic agent, is a member of the group of benzodiazepines, which was first marketed as Valium. Diazepam (DZ) is readily absorbed in the gastro-intestinal tract and metabolized in the liver. It is widely used as an effective drug against many manifestations such as anxiety, panic attacks, insomnia, seizures, muscle spasms, restless leg syndrome, alcohol withdrawal, and opiate withdrawal syndrome [4-5].

A review of the literature reveals that there are not many investigations done on the kinetics and mechanism of the DZ oxidation by NBS in acid solutions. However, a systematic kinetic study of the mechanism of the DZ oxidation has been reported using the N-haloamine, namely, sodium N-chlorobenzenesulfonamide [6]. In view of the lack of literature reports on the oxidation of DZ by N-halogenated imides, we have selected NBS as the oxidant to elicit the plausible mechanistic pathway of the oxidation reaction.

2. EXPERIMENTAL

2.1 Materials

N-Bromosuccinimide was obtained by Merck, India. The compound purity was checked iodometrically and by IR spectrum. An aqueous solution of NBS was freshly prepared each day and its concentration was checked by the iodometric titration against a standard thiosulfate solution using starch indicator near the endpoint. It was preserved in brown bottles to prevent its photochemical deterioration. DZ obtained from Ray Chemicals, India was recrystallized before use. All other reagents, namely, hydrochloric acid, mercury(II) acetate, diethyl ether, petroleum ether, *n*-butanol, methanol, silica gel, iodine, chloroform, sodium chloride, deuterated chloroform, *n*-hexane, dichloromethane and sodium perchlorate of Analar grade were obtained from SD Fine-Chem Ltd. Potassium bromide used in making pellets of samples for obtaining IR spectra was heated to 120 °C in an oven and cooled down to lab temperature in a desiccator prior to its use. Double distilled water was used throughout the investigation.

2.2 Instrumentation

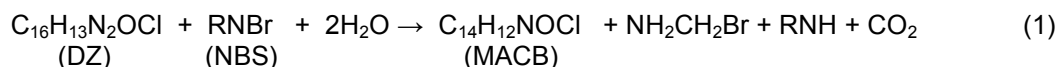
Fourier transform IR spectra were recorded on a Nicolet Impact 400D instrument, using KBr pellets. Nuclear magnetic resonance spectra were recorded on a Bruker SF 400 MHz at room temperature, peaks are reported in ppm and referenced to tetramethylsilane (TMS) as internal standard; coupling constants (J) are reported in Hz. Mass spectra were recorded on a Shimadzu SQP 5000 GC-MS spectrometer, employing an electron impact (EI) ionization chamber operating at 70 eV, a DB-I (J and W Scientific) GC capillary column operating in the temperature range of 80 to 250 °C, and a class k 54 k software data processing system.

2.3 Kinetic Measurements

Kinetic measurements were performed in glass-stoppered Pyrex boiling tubes coated black to eliminate photochemical effects. The reaction was carried out under pseudo-first order conditions of $[DZ]_0 \gg [NBS]_0$. Solutions of appropriate amounts of DZ, HCl and water (the latter to maintain a constant volume) were mixed and thermostated at a constant temperature (i.e., 313 K). A measured amount of the NBS solution, also thermostated at the same temperature, was rapidly added to the tube and mixed. The progress of the reaction was monitored by iodometrically titrating (against a standardized thiosulfate solution using starch indicator near the endpoint) the unreacted NBS in measured aliquots of the reaction mixture withdrawn at different time intervals. The course of the reaction was studied up to 75% completion. Pseudo-first order rate constants (k' or k_{obs}) determined were reproducible within a relative error of $\pm 3\%$.

2.4 Reaction Stoichiometry

Reaction mixtures of varying ratios of NBS and DZ under the condition of $[NBS] \gg [DZ]$ were equilibrated in HCl solution at 313K for 24 hours. Determination of unreacted NBS showed that one mole of DZ consumed one mole of NBS. The following stoichiometric equation represents the reaction:



where $R = (CH_2CO)_2$.

2.5 Product Analysis

The reaction products were extracted thrice with diethyl ether. The combined extract was evaporated and subjected to the column chromatography on silica gel (60-200 mesh) using chloroform for gradient elution (from *n*-hexane to chloroform). Products were further purified by recrystallization. Succinimide (RNH), which is the reduction product of NBS, was detected by thin-layer chromatography using petroleum ether-chloroform-*n*-butyl alcohol (2:2:1 v/v/v) as the mobile phase and iodine as the detection agent. Succinimide was also confirmed by IR: ν_{max}/cm^{-1} 3450 br (NH) and 1698 (CO). The other products were characterized as methyl aminochlorobenzophenone (MACB), N-bromomethanamine (NH_2CH_2Br) and CO_2 . The product, CO_2 , was identified using the conventional lime water test. N-bromomethanamine was identified by the Beilstein's test and diazotization. The product MACB was confirmed by the following analytical data: IR: ν_{max}/cm^{-1} 3338m (NH), 1621 (CO), and 710s (C-Cl). NMR: δ_H/ppm (400 MHz, $CDCl_3$, TMS) 8.45 (br s, 1H; NH), 6.70-7.70 (m, 8H; Ph), and 2.95 (d, $J =$

5 Hz, 3H; Me). MS (EI, 70 eV): m/z 245 (M^+), 229 ($M^+ - CH_3 - H$), 210 ($M^+ - Cl$), and 168 ($M^+ - Ph$).

3. RESULTS

The oxidation of DZ by NBS was carried out at a constant temperature in aqueous HCl solutions. Since the reaction was found to be facile in acid medium, a detailed kinetic study of the oxidation of DZ was made.

3.1 Effect of Varying Oxidant Concentration on the Rate

Kinetics of oxidation of DZ by NBS was studied at various initial concentrations of NBS [$1.00 \times 10^{-3} - 10.00 \times 10^{-3}$ M] at 313K keeping the concentration of DZ [1.00×10^{-2} M] and HCl [1.00×10^{-1} M] constant. Plots of $\log [NBS]$ vs. time were linear indicating a first-order dependence of the rate on [NBS]. The constancy of k' values at different concentrations of the oxidant NBS (Table 1, Fig.1) is an additional evidence for the pseudo-first order dependence of the rate on [NBS].

Table 1. Effect of varying concentrations of reactants on the reaction rate at 313K

$10^3[NBS]$ (M)	$10[HCl]$ (M)	$10^2[DZ]$ (M)	$10^5 k'$ (s^{-1})
1.00	1.00	1.00	20.2
1.00	1.00	2.00	28.9
1.00	1.00	3.00	39.7
1.00	1.00	4.00	46.4
1.00	1.00	5.00	54.8
1.00	0.50	1.00	13.4
1.00	1.00	1.00	20.0
1.00	1.50	1.00	28.0
1.00	2.00	1.00	33.7
1.00	2.50	1.00	41.2
1.00	1.00	1.00	19.9
2.50	1.00	1.00	20.0
5.00	1.00	1.00	20.0
7.50	1.00	1.00	20.1
10.0	1.00	1.00	20.0
1.00	1.00	1.00	20.1 ^a
1.00	1.00	1.00	20.0 ^b
1.00	1.00	1.00	20.0 ^c

^a 1.00×10^{-2} M [RNH]; ^b0.100 M [NaClO₄]; ^c0.100 M [Hg(OAc)₂]

3.2 Effect of Varying Diazepam on the Rate

The oxidation was carried out with varying concentrations of DZ [$1.00 \times 10^{-2} - 5.00 \times 10^{-2}$ M] while keeping constant the temperature and the concentrations of NBS [1.00×10^{-3} M] and HCl [1.00×10^{-1} M]. The rate of reaction increased with increasing [DZ]. A plot of $\log k'$ vs. $\log [DZ]$ was linear with a slope of 0.57 (Fig.1), indicating a fractional-order dependence of the rate on [DZ].

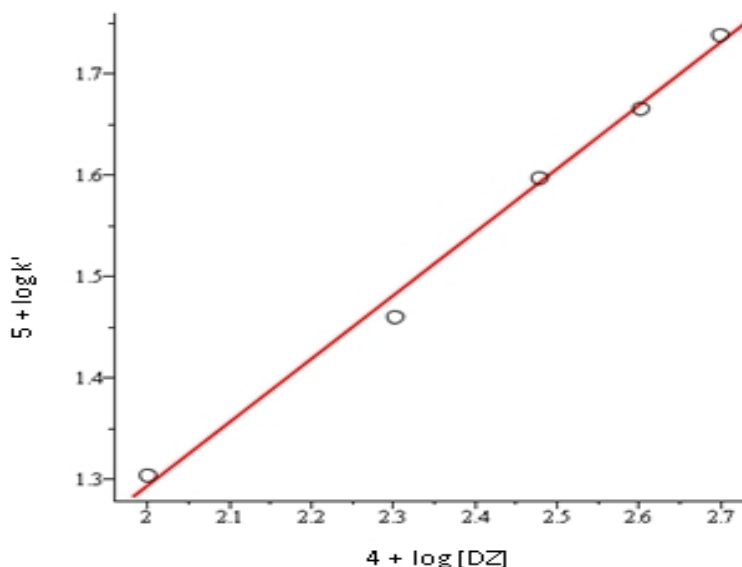


Fig. 1. Plot of $\log k'$ vs. $\log [DZ \text{ or } S]$

3.3 Effect of Varying HCL Concentration on the Rate

The reaction was carried out with $[1.00 \times 10^{-3} \text{ M}]$ oxidant and $[1.00 \times 10^{-2} \text{ M}]$ substrate in the presence of varying concentrations of HCl $[0.500 \times 10^{-1} - 2.50 \times 10^{-1} \text{ M}]$ at 313K. The rate increased with the increase in $[HCl]$ (Table 1). A plot of $\log k'$ vs. $\log [HCl]$ was linear with a slope of 0.76 (Fig.2), showing a fractional-order dependence of the rate on $[HCl]$.

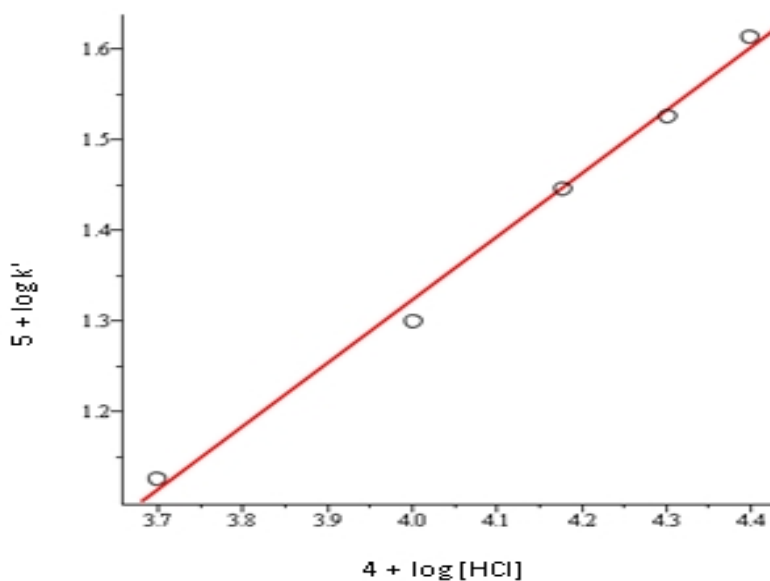


Fig. 2. Plot of $\log k'$ vs. $\log [HCl]$

3.4 Effect of Varying $[H^+]$ and $[Cl^-]$ on the Rate

In order to determine the order of the reaction with respect to $[H^+]$ and $[Cl^-]$ separately, the reaction was also studied by varying the concentration of one ion while keeping the concentration of the other constant. The effect of $[H^+]$ on the rate was studied by adding HCl at constant high $[Cl^-]$ maintained with NaCl and the effect of $[Cl^-]$ on the rate was studied by varying $[NaCl]$ at constant $[H^+]$. The plot of $\log k'$ vs. $\log [H^+]$ was linear with a slope of 0.51 (plot not shown), showing a fractional-order dependence of the rate on $[H^+]$ and the plot of $\log k'$ vs. $\log [Cl^-]$ was linear with a slope of 0.29 (plot not shown), showing a fractional-order dependence of the rate on $[Cl^-]$.

3.5 Effect of Varying Solvent Polarity and Dielectric Medium

The reaction of DZ [1.00×10^{-2} M] with NBS [1.00×10^{-3} M] was carried out in methanol-water mixtures of various compositions (% v/v) containing HCl [0.100 M] at 313K. The reaction rate increased with increase in methanol content (i.e., decrease in dielectric constant D) in the solvent medium (Table 2 and Fig.3). The D values were obtained from the literature [7].

Table 2. Effect of solvent composition on the reaction rate

% MeOH (v/v)	D*	$10^5 k' (s^{-1})$
0	76.73	19.9
5	74.55	23.3
10	72.37	28.9
20	67.48	54.7
30	62.71	63.2

*Dielectric constant (D) values were taken from Reference 7

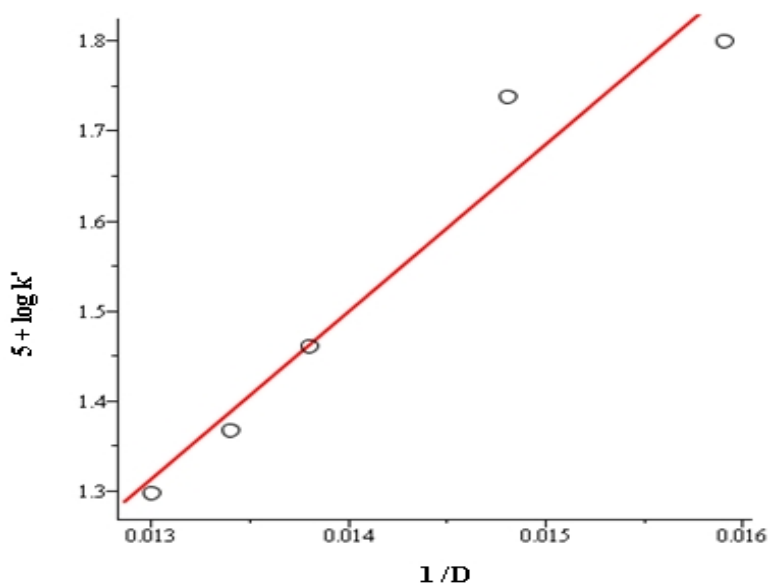


Fig. 3. Plot of $\log k'$ vs. $1/D$

3.6 Effect of Varying Ionic Strength on the Rate

The ionic strength of the solvent medium varied by adding NaClO_4 showed no significant effect on the reaction rate (Table 1). Hence, no attempt was made to keep the ionic strength constant for all other kinetic runs.

3.7 Effect of Varying Succinimide Concentration on the Rate

Addition of RNH, the reduction product of the oxidant NBS had no significant effect on the reaction rate (Table 1).

3.8 Effect of Varying $\text{Hg}(\text{Oac})_2$ Concentration on the Rate

The effect of mercury(II) acetate on the rate was found to be negligible (Table 1). The function of the added mercury(II) ions was to fix up Br^- ions formed in the course of the reaction.

3.9 Effect of Temperature

The rate constants (k') of the reaction were determined at different temperatures (293-333 K). From the linear Arrhenius plot of $\log k'$ vs. $1/T$ (Fig. 4 above) and the Eyring plot of $\log k'/T$ vs. $1/T$ the activation parameters, namely, energy of activation (E_a), enthalpy of activation (ΔH^\ddagger), entropy of activation (ΔS^\ddagger), and Gibbs free energy of activation (ΔG^\ddagger) along with the Arrhenius factor (A) were obtained (Table 3).

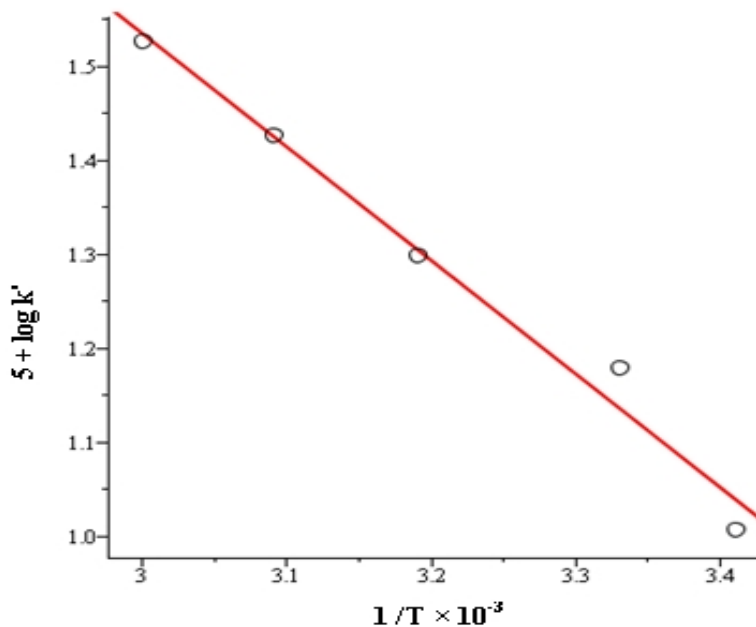


Fig. 4. Plot of $\log k'$ vs. $10^3/T$

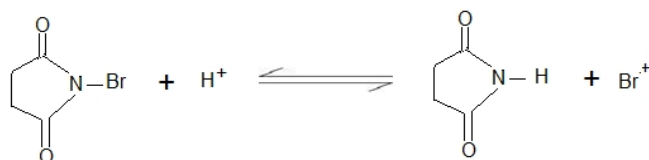
Table 3. Rate constants at varying temperatures and activation parameters

Temperature (K)	$10^5 k' (s^{-1})$	Activation parameter
293	10.2	$E_a (kJ mol^{-1})$ 23.0
303	15.2	$\Delta H^\ddagger (kJ mol^{-1})$ 20.4
313	20.0	$\Delta G^\ddagger (kJ mol^{-1})$ 98.9
323	26.9	$\Delta S^\ddagger (J.K^{-1} mol^{-1})$ -251
333	33.7	log A 8.45

4. DISCUSSION

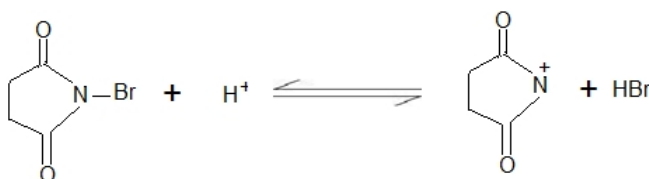
The oxidant NBS exists in different forms in acidic and basic solutions. In alkaline solution, its reactive species are NBS, HOBr and BrO^- while in acidic medium, the reactive species are NBS itself, Br^+ and the protonated species (RN^+HBr).

The reactive species is known to exist in the following equilibrium [8]:



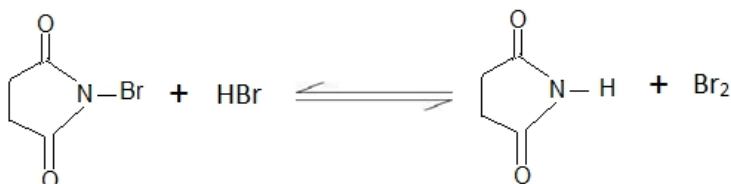
In the present investigation, it was found that the added succinimide had negligible effect on the reaction rate. This excludes the possibility of the above equilibrium, where Br^+ acts as the oxidizing species, before the rate determining step in the mechanism of oxidation.

Many investigations on the oxidation of organic substrates by NBS assume that the molecular NBS acts only through its positive polar end [9-10].

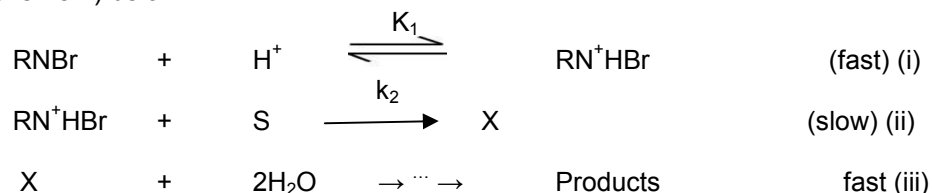


But in the present study, $[H^+]$ is proportional to the rate of reaction. Hence, RN^+HBr is the active oxidizing species. This makes it apparent that the role of pH of the reaction medium is crucial in carrying out the reaction.

All oxidation reactions of NBS have been made in the presence of mercury(II) acetate [11]. It acts as a scavenger for Br^- thereby suppressing the oxidation by Br_2 which is formed by the reaction of NBS with HBr as shown below.



Based on the preceding facts, the proposed DZ oxidation mechanism is presented in (Scheme 1) below.



Scheme 1. Mechanism of oxidation of DZ (S) by NBS (RNBr) in acid medium

From the rate determining or slow step in (Scheme 1),

$$\text{rate} = k_2 [\text{RN}^+\text{HBr}][\text{S}] \quad (2)$$

The total effective concentration of the oxidizing agent is given by

$$[\text{NBS}]_t = [\text{RNBr}] + [\text{RN}^+\text{HBr}] \quad (3)$$

Substitution for [RNBr] from fast the pre-equilibrium [step (i)] in eq. (3) leads to,

$$\begin{aligned}
 [\text{NBS}]_t &= [\text{RN}^+\text{HBr}] + [\text{RN}^+\text{HBr}] / K_1[\text{H}^+] \\
 \text{Or } [\text{NBS}]_t &= \{K_1[\text{H}^+][\text{RN}^+\text{HBr}] + [\text{RN}^+\text{HBr}]\} / K_1[\text{H}^+]
 \end{aligned} \quad (4)$$

Rearrangement of eq (4) results in eq (5),

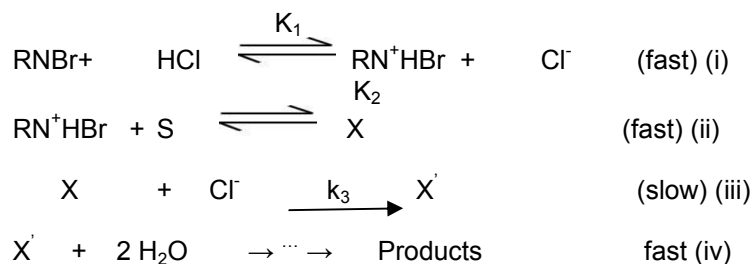
$$[\text{RN}^+\text{HBr}] = K_1[\text{NBS}]_t[\text{H}^+] / (K_1[\text{H}^+] + 1) \quad (5)$$

The combination of eq. (5) with eq. (2) gives the following rate law [eq. (6)]:

$$\text{rate} = K_1 k_2 [\text{H}^+][\text{NBS}]_t[\text{S}] / (K_1[\text{H}^+] + 1) \quad (6)$$

The derived rate law, which is consistent with the experimental rate law, reinforces the mechanism in (Scheme 1).

In the presence of Cl^- ions at constant $[\text{H}^+]$, (Scheme 2) is proposed for the reaction mechanism.



Scheme 2. Reaction mechanism of DZ or S oxidation by NBS in acid medium in the presence of Cl^-

From the slow step of (Scheme 2),

$$\text{rate} = k_3[X][\text{Cl}^-] \quad (7)$$

The total effective concentration $[\text{NBS}]_t$ is given by

$$[\text{NBS}]_t = [\text{RNBr}] + [\text{RN}^+\text{HBr}] + [X] \quad (8)$$

Substitutions for $[\text{RNBr}]$ and $[\text{RN}^+\text{HBr}]$ from the two fast equilibria [steps (i) and (ii)] in (Scheme 2) in eq. (8) lead to,

$$[\text{NBS}]_t = [X] \{ [\text{Cl}^-] + K_1[\text{HCl}] + K_1K_2[\text{HCl}][\text{S}] \} / K_1K_2[\text{HCl}][\text{S}] \quad (9)$$

Solving eq. (9) for $[X]$ gives,

$$[X] = K_1K_2 [\text{NBS}]_t [\text{HCl}][\text{S}] / \{ [\text{Cl}^-] + K_1[\text{HCl}] + K_1K_2[\text{HCl}][\text{S}] \} \quad (10)$$

Substitution for $[X]$ from eq. (10) into eq. (7) leads to the rate law (eq. (11)).

$$\text{rate} = K_1K_2k_3[\text{NBS}]_t[\text{S}][\text{H}^+][\text{Cl}^-] / \{ [\text{Cl}^-] + K_1[\text{H}^+] + K_1K_2[\text{S}][\text{H}^+] \}$$

Or

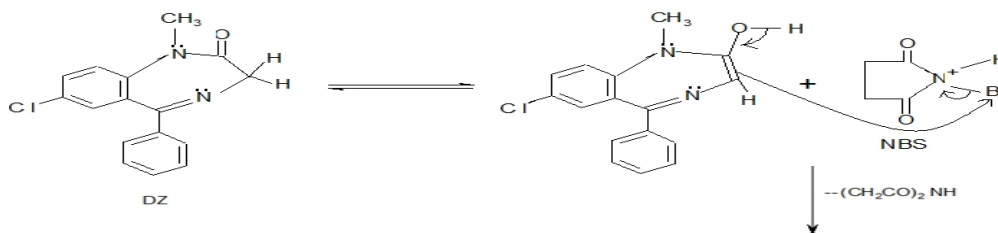
$$\text{rate} = K_1K_2k_3[\text{NBS}]_t[\text{S}][\text{H}^+][\text{Cl}^-] / \{ [\text{Cl}^-] + K_1[\text{H}^+]\{ 1 + K_1[\text{S}] \} \} \quad (11)$$

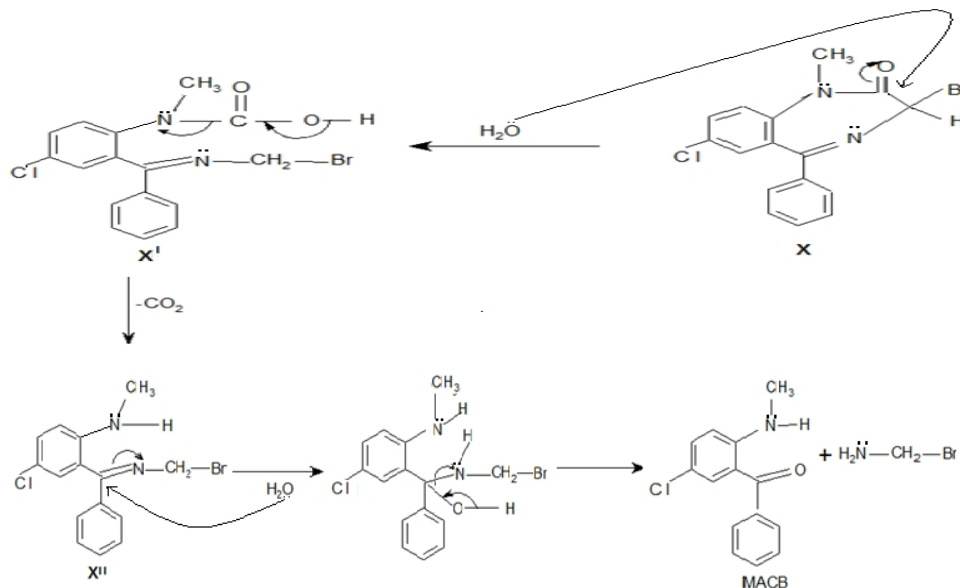
Here the acid, HCl, is denoted by $[\text{H}^+]$.

The rate law (eq.11) clearly supports the experimental kinetic results such as the first-order dependence of the rate on $[\text{NBS}]$ and a fractional-order each on $[\text{S}]$, $[\text{H}^+]$, and $[\text{Cl}^-]$.

A detailed mode of oxidation of DZ by NBS in acid solutions is presented in (Scheme 3). The protonated NBS reacts with the substrate in the enol form in a fast equilibrium step to give the intermediate X. Furthermore, bromination is not possible as the geminal dibromides are sterically hindered [12]. The intermediate X undergoes hydrolysis to give X'' via X' . Hydrolysis of X' leads to the decomposition forming the major end products, MACB and N-bromomethanamine.

The permittivity (D) of the solvent medium was varied by adding different amounts of MeOH (0-30% v/v) to the reaction mixture. The effect of solvent on the reaction kinetics has been described in the literature [13-17]. An increase in the MeOH content in the reaction medium leads increases the reaction rate, which is consistent with the expected interactions between the neutral substrate and the protonated oxidant species in the slow step in the reaction mixture of low D. Hence, it is seen that the rate increases with a decrease in the dielectric constant of the medium (Fig. 3).





Scheme 3. Detailed mechanistic scheme for the oxidation of DZ by NBS in acid solutions

For the limiting case of zero angle approach between two dipoles or an ion-dipole system, it is shown [18] that a plot of $\log k$ vs. $1/D$ gives a straight line with a positive slope for the positive ion-dipole interaction and a negative slope for the negative ion-dipole interaction. The proposed mechanistic Schemes 1- 3 are supported by the above positive ion-dipole interaction step.

The solvent effect agrees with the charge dispersion going into the transition state. The mechanism is also supported by a moderate value of energy of activation, a highly positive free energy of activation and a modest positive value of enthalpy of activation (Table 3) indicating that the transition state is highly solvated. The positive enthalpy of activation is probably due to changes in solvation going from the quaternary ammonium cation to a dispersed/charged transition state. The negative entropy of activation suggests the formation of a rigid transition state via an associative mechanism involving the loss of degrees of freedom.

5. CONCLUSION

The oxidation of DZ by NBS in aqueous acid medium has been kinetically studied. The stoichiometry of the reaction was found to be 1:1 and the oxidation products were identified by spectral studies. Activation parameters were computed and the observed kinetic results support the suggested mechanism and the derived rate law.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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