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Oxidation of Acetaminophen by N-Bromosuccinimide: A Kinetic and Mechanistic Study

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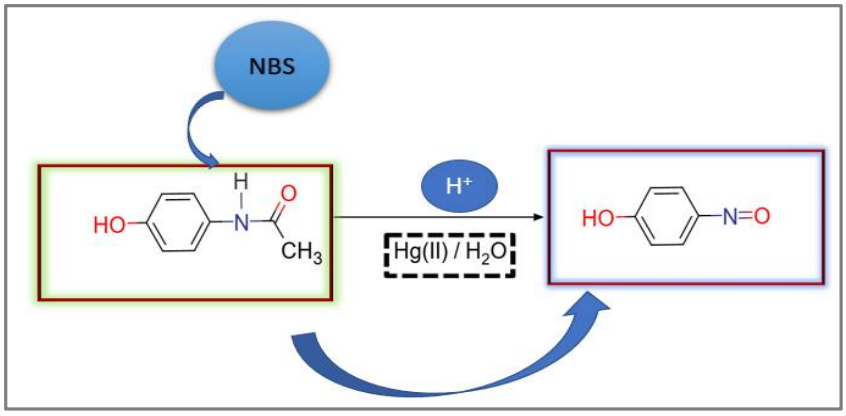
ABSTRACT

The kinetics and mechanism of oxidation of Acetaminophen (commonly known as Paracetamol) by N-Bromosuccinimide (NBS) has been studied in acidic medium at 313 K. The reaction exhibits first order in [NBS] and fractional order each in [acetaminophen] and [acid]. No change in reaction rate, when subjected to changes in concentration of succinimide, the reduction product of NBS. Variation of ionic strength had no effect on the reaction rate. The decrease in the rate of reaction with an increase in dielectric constant of the medium was observed. The reaction is failed to induce the polymerization of acrylonitrile. The stoichiometry of the reaction has been determined and oxidation products were identified and characterized. The reaction was studied at seven different temperatures and the activation parameters were obtained from Arrhenius plot. Protonated NBS has been postulated as reactive oxidizing species in acidic medium. The observed results have been explained by the proposed plausible mechanism which involves the decomposition of acetaminophen-NBS complex in the slow step, resulting in the corresponding quinone oxime. Rate law has been derived.

Graphical Abstract



Keywords: Acetaminophen, N-bromosuccinimide, Oxidation, Kinetics, Mechanism.

INTRODUCTION

Acetaminophen (commonly called as Paracetamol) is a well-known drug containing acetamide and hydroxyl groups and is known for its analgesic and antipyretic activity. The metabolites of paracetamol, N-acetyl-p-benzoquinone imine (NAPQI) and p-benzoquinone are responsible for decrease in pain and fever. It exerts inhibitory action on COX-2 by reducing the availability of co-substrate for the enzymatic action of COX-2. One of the metabolite, NAPQI inhibits cysteine proteases which are involved in the generation of inflammatory interleukins IL-1β and IL-6 [**1**]. It acts by inhibiting the transmission of pain impulses to higher centres. Though it acts as analgesic and antipyretic drug it lacks in anti-inflammatory activity [**2**]. Through various metabolic pathways acetaminophen is converted into non-toxic products in the liver and is eventually excreted by the kidneys. However, overdoses may cause liver and renal toxicity due to the binding of one of the metabolite quinine imine to proteins [**3**] which leads to the depletion of glutathione and also covalent binding of excess metabolites to the vital constituents of the cell [**4**].

Acetaminophen has been reported to be present in waste water [**5-8**], therefore several oxidation studies were made for the removal of acetaminophen from the waste water to understand the mechanism of decomposition and to know the probable path of oxidation. As a part of these studies, attention has been given by several workers in the oxidation of acetaminophen [**9-17**] by various oxidizing agents.

Among many N-halo compounds available, N-halomides are chosen as oxidants for the oxidation of many substrates due to their ability to produce halonium cations, hypohalite species and nitrogen anion which act as both bases and nucleophiles [**18**]. A well-known N-halomide is N-Bromosuccinimide (NBS), which acts as a source of positive halogen has gained considerable attention due to its capacity to oxidize a wide variety of substrates in both acidic and alkaline medium [**19-28**]. The nature of active oxidizing species and the mechanism depends on the nature of the halogen atom, the groups attached to the nitrogen and the reaction condition. The species responsible for such oxidizing character may be different depending on the *p*H of the medium. Although the N-bromosuccinimide oxidation of a large variety of organic compounds has been studied, there seems to be no report on a systematic kinetic study of the oxidation of acetaminophen by N-bromosuccinimide.

Therefore, in the present study, we aim to investigate thoroughly the kinetics and mechanistic aspects of the reaction between acetaminophen and N-Bromosuccinimide in sulphuric acid medium, to identify the active species of the substrate, oxidant and oxidation products and evaluate the related kinetic and thermodynamic parameters of the reaction.

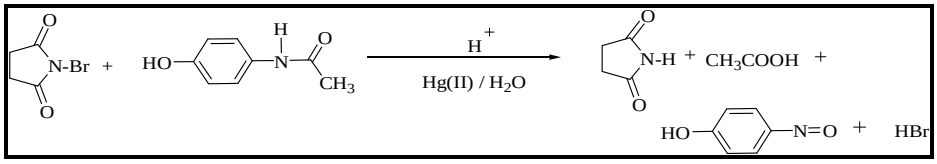
MATERIALS AND METHODS

All the chemicals used were of reagent grade. Acetaminophen was purchased (Sigma-Aldrich) and used without further purification. All other reagents were of analytical grade. Purity of the substrates was checked by the melting point. Standard solution of NBS was prepared and its purity was checked iodometrically. Solutions were prepared with either doubly distilled water or purified acetic acid and were standardized by known methods. Fresh solutions were used for each kinetic run. Acetic acid (BDH) was purified by refluxing with chromic acid and acetic anhydride for 6 h and then distilled and used to study the effect of solvent polarity on the reaction medium. The ionic strength was maintained using sodium sulphate, and to vary hydrogen ion concentration, sulphuric acid was used. Acrylonitrile was used directly as received to study the intervention of free radical formation during the reaction. Separation and identification of organic intermediates in the reaction were performed using high performance liquid chromatography (HPLC).

Kinetic Measurements: All the kinetic measurements were performed under pseudo-first-order conditions with [Acetaminophen] >> [NBS]. The reaction was initiated by the addition of known amounts of oxidant to reaction mixtures containing the required amounts of substrate, sulphuric acid,

and water in glass–stoppered Pyrex boiling tubes that were thermostated at the same temperature. The progress of the reaction was monitored by iodometric determination of unconsumed [NBS] in known aliquots of the reaction mixtures at different time intervals. However, before adopting iodometric method, it was ensured that the presence of acetaminophen in the quenching solution of potassium iodide did not change the oxidant (NBS) titre value. The course of the reaction was studied for at least two half–lives. The rate constants (k, s^{-1}) were determined from the pseudo-first-order plots of log [NBS] against time. The pseudo-first-order plots were linear ($r^2 \geq 0.99$) for more than 80 % completion of the reaction and the rate constants (k, s^{-1}) were reproducible within ± 5%.

Stoichiometry and product analysis: Different reaction mixtures with different sets of reactants containing various amounts of NBS and acetaminophen at fixed concentration of acid, ionic strength and temperature were allowed to react for 24 h in an inert atmosphere. After completion of the reaction, the unreacted N-Bromosuccinimide (NBS) was estimated iodometrically. The obtained results indicated that one mole of NBS consumed one mole of acetaminophen as represented in the following equation.



The above stoichiometric equation is consistent with the results of product analyses. The oxidation product of acetaminophen was identified as the quinone oxime by both spectral and chemical analyses. The yield was about 91%. The melting point of the recrystallized quinone oxime was found to be 131°C (lit. m.p = 132°C). The formation of quinone oxime was confirmed by IR Spectral (KBr) data i) a band at (ν)1652 cm^{-1} due to –C=O stretching (ii) a band at (ν)1615 cm^{-1} due to –C=N stretching of oxime (iii) a band at (ν) 3332 cm^{-1} due to O–H stretching. Similar oxidation product of acetaminophen with different experimental condition was reported earlier [29]. The reduction product of NBS, succinimide (NH), was detected by the method reported elsewhere [30]. Formation of pale-yellow precipitate by the addition of silver nitrate solution indicates the formation of silver bromide, suggesting that bromide ion is obtained as one of the reaction products.

RESULTS AND DISCUSSION

Role of mercuric acetate: Mercury (II) can act as a homogeneous catalyst, co-catalyst, oxidant [31] and scavenger for bromide ions. In the present study, mercury (II) acetate acts as a scavenger to fix up bromide ions formed in the course as $HgBr_2$ or $HgBr_4^{2-}$. To avoid any possible bromine oxidation, an optimum concentration (0.005 $mol.dm^{-3}$) of mercuric acetate was employed to eliminate bromide ion in the reaction without perturbing the kinetic results, thus ensuring that oxidation took place purely through NBS itself [32]. All the kinetics studies were made with [mercuric acetate] greater than [NBS] which simply means that Br_2 oxidation was completely suppressed. The mercuric acetate was used over a wide concentration range of 0.001–0.01 $mol.dm^{-3}$ and has no effect on the rate of reaction.

Effect of substrate and oxidant concentration: At fixed concentration of other reactants and when [acetaminophen] is in 10–fold excess over [NBS], the disappearance rate of [NBS] followed first-order rate law as was observed from the log initial rate (with respect to concentration/time) versus log [NBS] ($r > 0.998$) for more than three half-lives of the reaction. Further, the pseudo–first-order rate constant (k, s^{-1}), evaluated from the slopes of such plots remained unchanged (Table 1) with the variation of [NBS], confirming the first order dependence of the rate on [NBS].

Under the same experimental conditions, the rate of the reaction increased linearly with increase in [acetaminophen] (Table 1) and the log–log plot of k versus [substrate] were linear ($r \geq 0.995$, $s \leq$

0.03) with slope values of 0.58 (Figure 1a). Further, dependence of *k* value on the initial substrate concentration was consistent with the Lineweaver–Burk kinetics (Figure1b).

Table 1. Dependence of rate on the factors influencing the oxidation of acetaminophen by N-Bromosuccinimide (NBS) in acidic medium at 313 K

Non-variable constituent (mol.dm^{-3})	Variable constituent (mol.dm^{-3})	$10^2 \times k$ (s^{-1})
	[N-Bromosuccinimide]	
[acetaminophen] = 10.0 ×10^{-3}	5.0 × 10^{-4}	4.60
[H_2SO_4] = 1.0	7.5 × 10^{-4}	4.59
AcOH–H_2O = 1:1 (% *v*/*v*)	10.0 × 10^{-4}	4.60
[$Hg(OAc)_2$] = 5.0 × 10^{-3}	15.0 × 10^{-4}	4.62
	20.0 × 10^{-4}	4.59
	25.0 × 10^{-4}	4.61
	[acetaminophen]	
[NBS] = 10.0 ×10^{-4}	2.5 × 10^{-3}	1.96
[H_2SO_4] = 1.0	5.0 × 10^{-3}	2.87
AcOH–H_2O = 1:1 (% *v*/*v*)	7.5 × 10^{-3}	3.76
[$Hg(OAc)_2$] = 5.0 × 10^{-3}	10.0 × 10^{-3}	4.60
	15.0 × 10^{-3}	5.75
	20.0 × 10^{-3}	6.38
	25.0 × 10^{-3}	7.46
	30.0 × 10^{-3}	8.34
	[H_2SO_4]	
[NBS] = 10.0 ×10^{-4}	0.25	2.30
[acetaminophen] = 10.0 ×10^{-3}	0.50	3.22
AcOH–H_2O = 1:1 (% *v*/*v*)	0.75	3.79
[$Hg(OAc)_2$] = 5.0 × 10^{-3}	1.00	4.60
	1.25	4.92
	1.50	5.06
	2.00	6.30
	AcOH–H_2O (%*v*/*v*)	
[NBS] = 10.0 ×10^{-4}	30-70 (53.18)*	3.45
[acetaminophen] = 10.0 ×10^{-3}	40-60 (46.48)	4.08
[H_2SO_4] = 1.0	50-50 (39.78)	4.60
[$Hg(OAc)_2$] = 5.0 × 10^{-3}	60-40 (33.08)	5.75
	70-30 (26.08)	6.90

*Parentheses values indicate the dielectric constant of the medium.

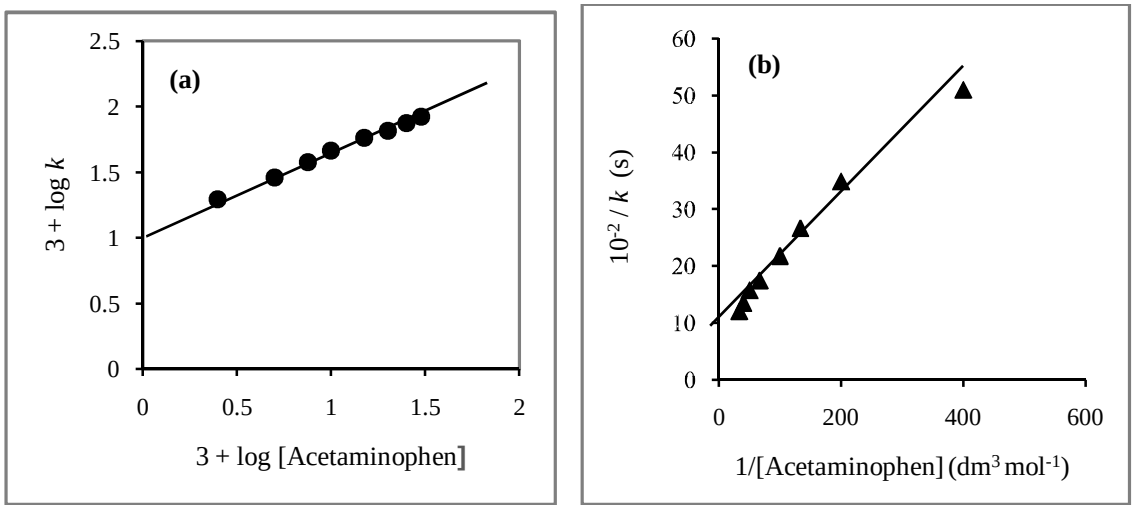


Figure 1(a). Plot between log *k* and log [Acetaminophen], (b) Plot between 1/*k* and 1/[Acetaminophen] for the reaction.

Effect of [acid]: The effect of [acid] on the reaction rate was studied in order to establish the active species of reactants present in the solution. At fixed concentrations of substrate (acetaminophen), NBS, and other conditions remaining constant, the reaction rate increased linearly with increase in [acid] (Table 1). The reaction order (Figure 2a) with respect to [H^+] ion is found to be fractional (0.49).

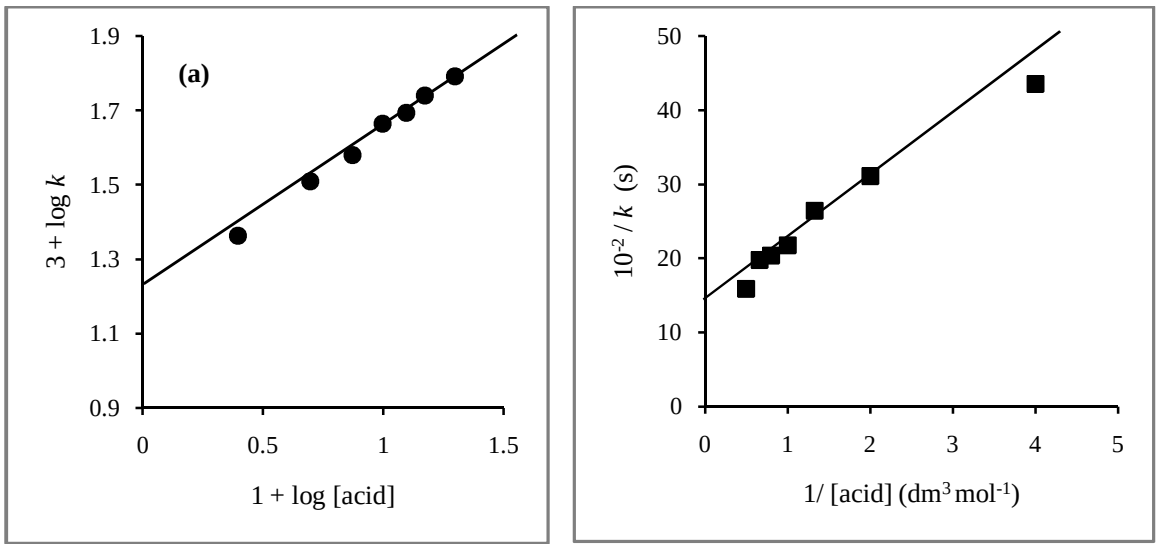


Figure 2(a). Plot between log *k* and log [acid], (b) Plot of 1/*k*against 1/[acid] under the conditions.

Effect of ionic strength and dielectric constant of the medium: The effect of ionic strength on the reaction rate was studied using Na_2SO_4, with other experimental conditions held constant. There was no significant effect of ionic strength on the reaction rate. The dielectric constant (D) of the medium (Table 1) was varied using different proportions of acetic acid from 30-70%. The D values were calculated from the equation $D = D_W V_W + D_A V_A$, where D_W and D_A are the dielectric constants of pure water and acetic acid respectively, and V_W and V_A are the volume fractions of components water and acetic acid respectively in the total mixture. The reaction rate increased with a decrease in dielectric constant of the medium. Plot of log *k* versus 1/D (Figure 3) was found to be linear with positive slope. Blank experiments performed showed that acetic acid was not oxidized significantly by NBS under prevailing conditions.

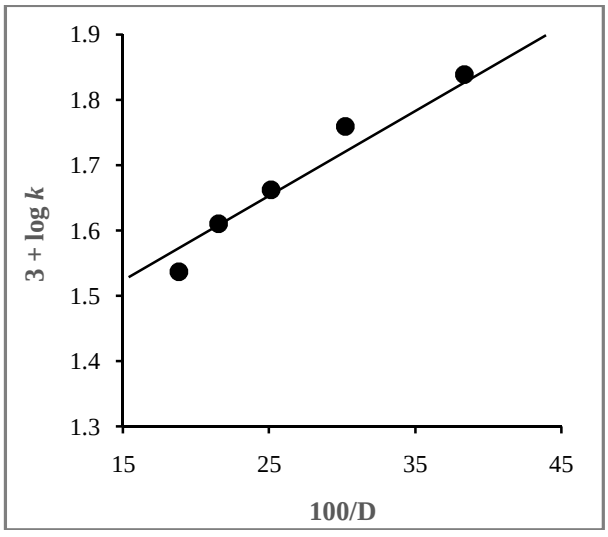


Figure 3. Plot of log *k* against 1/D under the conditions.

Effect of succinimide on the rate: The reaction was studied by varying the concentration of succinimide in the concentration range of 0.0025 to 0.025 mol.dm^{-3} and all other parameters being held constant, has no effect on the rate of reaction.

Test for Free Radicals: The reactions were studied in the presence of added acrylonitrile to understand the intervention of free radicals. There was no effect of added acrylonitrile (0.1–1.0 mol.dm^{-3}) on the reaction rate, and also no precipitate due to polymerization of acrylonitrile was observed, suggesting the absence of any free radical formation in the reaction. To confirm further, the absence of free radicals in the reaction pathway, the reaction was carried out in the presence of 0.05 mol.dm^{-3} of 2, 6-di-*t*-butyl-4-methylphenol (butylated hydroxyl toluene or BHT). It was observed that the BHT was recovered unchanged, almost quantitatively.

Effect of Temperature: The oxidation of acetaminophen was studied in the temperature range (Table 2) of 293–323 K and the activation parameters were evaluated from the slope of Arrhenius plot (Figure 4) of log *k* versus 1/T are: *E*a = 42.08± 1.5 kJ mole^{-1}; $\Delta H^{\neq}$ = 39.48 ± 1.5 kJ mole^{-1}; $\Delta S^{\neq}$ = – 147.62 J/K/mole and $\Delta G^{\neq}$ = 85.69 ± 1.2 kJ mole^{-1} at 313 K at concentrations of NBS = 10.00 × 10^{-4} mol/dm^{-3}, Acetaminophen = 10.00 × 10^{-3} mol.dm^{-3}; H_2SO_4 = 1.00 mol.dm^{-3}. Large negative value of entropy indicates that the complex is more ordered than the reactants.

Table 2. Influence of temperature on the rate of the reaction

Temp (K)	293	298	303	308	313	318	323
$k \times 10^2$ (s^{-1})	1.57	2.26	2.76	3.68	4.60	5.68	8.44

Experimental conditions:[Acetaminophen] =10.0 × 10^{-3} mol·dm^{-3}, [NBS] = 10.0 × 10^{-4} mol·dm^{-3}, [H_2SO_4] = 1.0 mol·dm^{-3}, [$Hg(OAc)_2$] = 5.0 × 10^{-3} mol·dm^{-3}

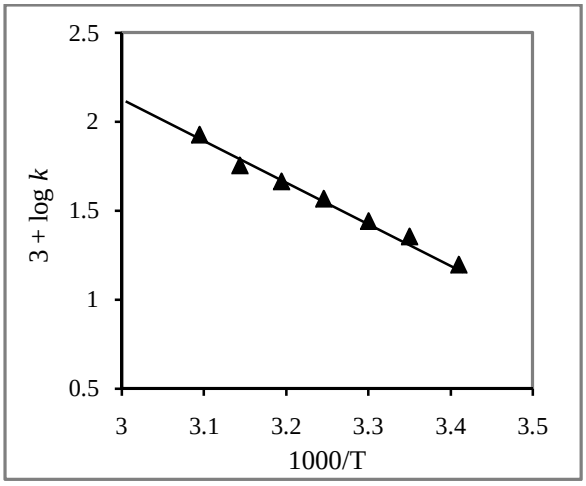


Figure 4. Arrhenius plot of log *k* versus 1/T.

Active species of the reactants and mechanism: N-Bromosuccinimide is a two-electron oxidant and active species of NBS involved in oxidation reactions are NBS itself or Br^+ or protonated NBS ($NBSH^+$) in acidic medium [**33–35**] and NBS, HOBr or OBr^- are the reactive species in alkaline solutions. As the reactions are carried out in acidic medium the following are the equilibria [**19-21**] that exists in the reaction system

$$NBS + H^+ \rightleftharpoons N^+BSH \quad \ldots(1)$$

$$NBS + H^+ \rightleftharpoons NSH + Br^+ \quad \ldots(2)$$

$$Br^+ + H_2O \rightleftharpoons H_2OBr^+ \quad \ldots(3)$$

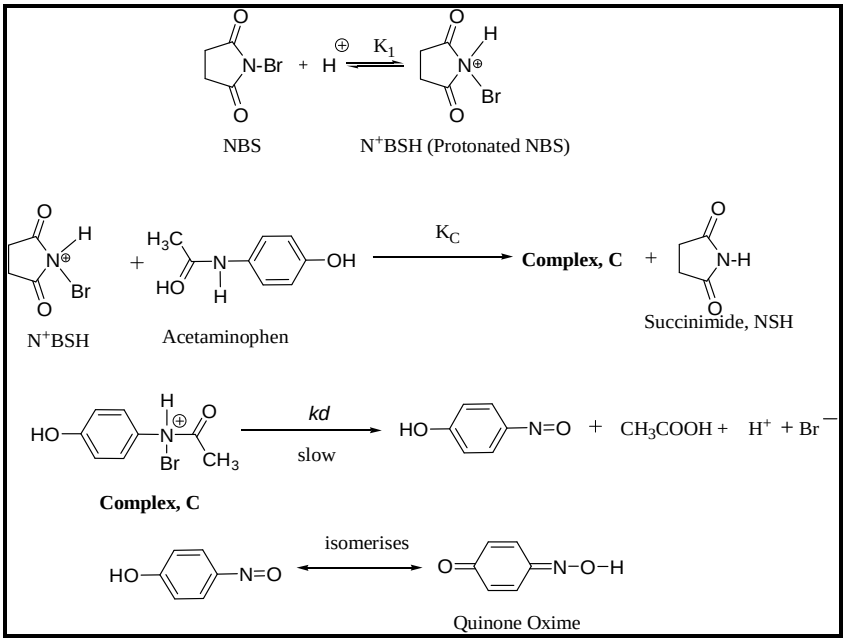
$$NBS + H_2O \rightleftharpoons NSH + HOBr \quad \ldots(4)$$

It may be pointed out that, all the kinetic studies have been made in the presence of mercury (II) acetate in order to avoid any possible bromine oxidation which may be produced as follows

$$NBS + HBr \rightarrow NSH + Br_2 \quad \ldots(5)$$

Mercuric acetate acts as a capturing agent for any bromide ions [36] formed in the reaction and exists as $HgBr_4^{2-}$ or unionized $HgBr_2$ and ensures that oxidation takes place purely through NBS. Remaining to be ensured are, the participation of either of Br^+ or HOBr or H_2OBr^+. The acceleration of reaction rate by an increase in the concentration of acid, which is attributed to the protonation equilibria of the oxidant and insignificant effect of added succinimide suggests that protonated N-Bromosuccinimide is the active oxidizing species of the NBS. Further, it is observed that the plot of log *k* against 1/D was found to be linear with a positive slope which indicates that the reaction is in between a positive ion and a neutral molecule. This is also evident from the negligible effect of variation in the ionic strength on the reaction rate, suggesting that the reaction is not in between charged species and is in between charged and uncharged species.

Among acetaminophen and NBS, the possibility of existence of acetaminophen with a positive charge has been ruled out because the *p*K value for the acetamide group of acetaminophen has been determined as 9.5 [37]. Hence, in acidic medium, this group will be in its neutral form. Thus, above experimental observations suggest the participation of NBS in the reaction in its protonated form. Therefore, the active species of the reaction are protonated NBS and acetaminophen in neutral form [17]. Based on the aforesaid, a probable mechanism for the oxidation of acetaminophen by NBS has been proposed (Scheme 1).



Scheme: Mechanism of oxidation of Acetaminophen.

The mechanistic pathway is demonstrated by (i) The formation of the active species of NBS, protonated NBS (N^+BSH) (ii) The complex formation between protonated NBS and acetaminophen (iii) The decomposition of the formed Complex, C is the rate-determining step as shown in Scheme 1 which is in accordance with the observed stoichiometry. Based on this, a rate law has been derived

which explains the fractional order in [H^+] and [acetaminophen] and absence of [NHS] effect on the rate of reaction.

Derivation of rate law: Based on the proposed mechanism rate law has been derived which is in accordance with the proposed mechanism. Taking all the steps of Scheme 1for the oxidation of acetaminophen and stoichiometry of the reaction, the following rate law Eq. 6 may be written in terms of loss of concentration of NBS.

$$\text{Rate} = \frac{-\text{d[NBS]}}{\text{dt}} = k_d[\text{Complex, C}] \qquad \ldots (6)$$

On the basis of steps in Scheme 1:

$$[\text{Complex C}] = K_c[\text{Acetaminophen}][N^+\text{BSH}] \quad \ldots (7)$$

$$[\text{Complex C}] = K_1K_c[\text{Acetaminophen}][\text{NBS}][H^+]$$

In terms of total NBS concentration, rate can be represented as:

$$\text{Rate} = \frac{-\text{d}\,[\text{NBS}]_T}{\text{dt}} = k_d[\text{Complex, C}] \qquad \ldots (8)$$

$$\text{Rate} = \frac{-\text{d}\,[\text{NBS}]_T}{\text{dt}} = k_dK_1K_c[\text{Acetmainophen}][\text{NBS}][H^+] \quad \ldots (9)$$

Since, NBS (N-Bromosuccinimide) is present in complexed and uncomplexed forms, at any time the total concentration of NBS can be given as Equitation 10.

$$[\text{NBS}]_T = [\text{NBS}] + [N^+\text{BSH}] + [\text{Complex, C}] \quad \ldots (10)$$

$$[\text{NBS}]_T = [\text{NBS}] + K_1[\text{NBS}][H^+] + [\text{Complex, C}]$$

$$[\text{NBS}]_T = [\text{NBS}] + K_1[\text{NBS}][H^+] + K_c[\text{Acetaminophen}][N^+\text{BSH}]$$

$$[\text{NBS}]_T = [\text{NBS}] + K_1[\text{NBS}][H^+] + K_1K_c[\text{Acetaminophen}][\text{NBS}][H^+]$$

$$[\text{NBS}]_T = [\text{NBS}][\{1 + K_1[H^+] + K_1K_c[\text{Acetaminophen}][H^+]\}] \quad \ldots (11)$$

Therefore,

$$[\text{NBS}] = \frac{[\text{NBS}]_T}{1 + K_1[H^+] + K_1K_c[\text{Acetaminophen}][H^+]} \qquad \ldots (12)$$

The rate law in terms of total NBS concentration can be given as:

$$\text{Rate}\ \frac{-\text{d}\,[\text{NBS}]}{\text{dt}} = \frac{k_dK_1K_c[\text{Acetaminophen}][\text{NBS}]_T\,[H^+]}{1 + K_1[H^+] + K_1K_c[\text{Acetaminophen}][H^+]} \qquad \ldots (13)$$

The rate law (Equation 13) is in accordance with the observed experimental results, wherein a first-order dependence on [NBS], and the order less than unity each in [acetaminophen] and [H^+] was observed.

$$\frac{\text{Rate}}{[\text{NBS}]_T} = k = \frac{k_d K_1 K_c [\text{Acetaminophen}][H^+]}{1 + K_1[H^+] + K_1 K_c [\text{Acetaminophen}][H^+]}$$

$$\frac{1}{k} = \frac{1}{k_d K_1 K_c [\text{Acetaminophen}][H^+]} + \frac{1}{k_d K_c [\text{Acetaminophen}]} + \frac{1}{k_d} \quad \ldots (14)$$

According to Eq. (14), the plots of 1/*k* versus 1/[acetaminophen] (at constant [H^+]) and 1/*k* against 1/[acid] (Figure 2b) (at constant [acetaminophen]) should be linear with a definite (the same) intercept on the 1/*k* axis. Such an observation supports the validity of the rate law and hence the proposed reaction mechanism (Scheme 1). The proposed mechanism is further supported by the observations made during the effect of solvent on the reaction rate. The increase in the oxidation rate with decrease in polarity of the medium as is evident from the positive slope value of log *k* against 1/D (Figure 3) plot suggests that the reaction is in between a positive ion and a neutral molecule and also indicates that the transition state is more polar than the reactants. The positive slope value also suggests an existence of charge separation in the transition state of the reaction. The observed high positive values of the enthalpy of activation $\Delta H^{\neq}$ and free energy of activation $\Delta G^{\neq}$ of the reaction suggest that the transition state is more solvated than the reactants. Larger negative value of $\Delta S^{\neq}$ value suggests loss of degrees of freedom upon the formation of a highly solvated and rigid transition state [**20, 38, 39**] indicating that complex is more ordered than the reactants and provides further support for a polar nature of the reaction, accompanied by a substantial loss of translational entropy due to solvation.

APPLICATION

Based on the obtained experimental results a mechanism for the oxidative degradation of Acetaminophen by N-Bromosuccinimide has been proposed which is found to be one of the efficient methods where the concentration of oxidant employed in the present work is very low in the range of 10^{-4} mol. dm^{-3}.

CONCLUSION

The kinetics and mechanism of oxidation of acetaminophen by N-Bromosuccinimide (NBS) has been investigated in sulphuric acid medium. Protonated NBS (N^+ BSH) is found to be the active species of the oxidant. The oxidation product was identified and is found to be quinone oxime. The reaction was carried out at seven different temperatures and thermodynamic parameters were evaluated and discussed. The observed results have been explained from proposed mechanism, and the rate law has been derived.

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REFERENCES

[1]. D. A. Andersson, C. Gentry, L. Alenmyr, D. Killander, S. E. Lewis, A. Andersson, B. Bucher, J. L. Galzi, O. Sterner, S. Bevan, E. D. Hogestatt, P. M. Zygmunt, TRPA1 mediates spinal antinociception induced by acetaminophen and the cannabinoid Δ9-tetrahydrocannabiorcol, *Nat. Commun.*,**2011**, 2(55), 1–11.

[2]. R. S. Borges, T. G. Barros, A. A. S. Veiga, A. S. Carneiro, C. A. L. Barros, A. B. F. Silva, A computational study for the antioxidant capacity increases in hydroxy-derivatives of paracetamol and salicylic acid, *Med. Chem. Res.*, **2015**, 24(9),3453–3459.

[3]. V. Fischer, P. R. West, L. S. Harman, R. P. Mason, Free-radical metabolites of acetaminophen and a dimethylated derivative, *Environ. Health. Perspect*, **1985**, 64**,** 127–137.
[4]. S. Garnayak, S. Patel, Oxidative Cleavage of Acetaminophen by Cetyltrimethylammonium Dichromate: A Mechanistic Study, *Ind. Eng. Chem. Res*., **2013**, 52, 13645−13653.
[5]. A. Liu, K. Wang, W. Chen, F. Gao, Y. Cai, X Lin, Y Chen, X. S. Xia, Simultaneous and sensitive voltammetric determination of acetaminophen and its degradation product for pharmaceutical quality control and pharmacokinetic research by using ultrathin poly (calconcarboxylic acid) film modified glassy carbon electrode, *Electro. Chim. Acta*, **2012**, 63 161–168.
[6]. N. Muir, J. D. Nichols, J. M. Clifford, J. Sykes, Comparative bioavailability of aspirin and paracetamol following single dose administration of soluble and plain tablets, *Curr. Med. Res. Opin*., **1997**, 13,491–500.
[7]. J. Li, Q. Ye, J. Gan, Degradation and transformation products of acetaminophen in soil, *Water. Res.*, **2014**, 49, 44–52.
[8]. J. R. Krzysztof, L. H. Britigan, G. T. Rasmussen, B. A. Wagner, P. Burns, B. E. Britigan, Acetaminophen stimulates the peroxidative metabolism of anthracyclines, *Arch. Biochem. Biophys.*, **2004**, 427, 16–29.
[9]. R. M. Mulla, G. Basavaraj, Kinetics of ruthenium(III)-catalysed oxidation of paracetamol by diperiodatonickelate(IV) in aqueous alkaline medium (stopped flow technique), *Appl. Catal A.*,**2006**, 314, 208–215.
[10]. T. S. Kiran, C. V. Hiremath, Kinetic, mechanistic and spectral investigations of ruthenium (III)/osmium (VIII)-catalysed oxidation of paracetamol by alkaline diperiodatoargentate(III) (stopped flow technique), *Appl. Catal A.*,**2006**, 305, 79–89.
[11]. T. S. Kiran, D. C. Hiremath, S. T. Nandibewoor, Oxidation of N-(4-hydroxyphenyl) acetamide (paracetamol) drug by diperiodatocuprate(III) in aqueous alkaline medium by stopped flow technique, *Z. Phys. Chem.*, **2007**, 221,501–517.
[12]. R. Andreozzi, V. Caprio, R. Marotta, D. Vogna, Paracetamol oxidation from aqueous solutions by means of ozonation and H_2O_2/UV system, *Water. Res.*, **2003**, 37, 993-1004.
[13]. M. Skoumal, P. L. Cabot, F. Centellas, C. Arias, R. M. Rodriguez, J. A. Garrido, E. Brillas, Mineralization of paracetamol by ozonation catalyzed with Fe^{2+}, Cu^{2+} and UVA light, *Appl. Catal B.*, **2006**, 66(3-4), 228–240.
[14]. A. K. Singh, R. Negi, B. Jain, Y. R. Katre, S. P. Singh, V. K. Sharma, Pd(II) Catalyzed oxidative degradation of paracetamol by chloramine-T in acidic and alkaline media, *Ind. Eng. Chem. Res.*,2011, 50(14) 8407–8419.
[15]. N. Jallouli, K. Elghniji, H. Trabelsi, M. Ksibi, Photocatalytic degradation of paracetamol on TiO_2 nanoparticles and TiO_2/cellulosic fiber under UV and sunlight irradiation, *Arab. J. Chem.*, **2017**, 10, S3640–S3645.
[16]. R. Negi, B. Jain,S. Singh, Kinetics and mechanistic study of oxidation of paracetamol: an accelerated catalytic approach, *S N. Appli. Sci.*,**2019**, 1, 1380 https://doi.org/10.1007/s42452-019-1365-8
[17]. J. D. Sawant, K. K. Patil, G. S. Gokavi, Kinetics and mechanism of oxidation of paracetamol by an Anderson-type 6-molybdocobaltate (III) in acidic medium, *Trans. Met. Chem.*, **2019**, 44, 153-159.
[18]. M. M. Campbell, G. Johnson, Chloramine T and related N-halogeno-N-metallo reagents, *Chem. Rev.*, **1978**, 78(1), 65–79.
[19]. A. K. Singh, R. Srivastava, S. Srivastava, J. Srivastava, S. Rahmai, B. Singh, N-Bromosuccinimide oxidation of maltose and d-galactose using chloro-complex of Rh(III) in its nano-concentration range as homogeneous catalyst: A kinetic and mechanistic study, *J Mol. Cat A: Chemical.*, **2009**, 310, 64-74.
[20]. A. A. P. Khan, A. Khan, M. Abdullah, A. S. A. Khan, Studies on the oxidation of levofloxacin by N-bromosuccinimide in acidic medium and their mechanistic pathway, *J. Mol. Liquids*.**2016**, 218, 604-610.

[21]. A. E. M. Abdel-Hady, Kinetics and mechanism of oxidation of L-Proline by N-Bromo succinimide in aqueous acidic medium, *Ind. Eng. Chem. Res*., **2011**, 50, 12421–12425.
[22]. V. Sumithra, C. Y. Wilson, D. Easwaramoorthy, A Kinetic and mechanistic study on the oxidation of 3-carboxy-3-hydroxy petanedioic acid in buffered medium, *Ind. Eng. Chem. Res.*, **2010**, 49, 9077–9081.
[23]. M. N. Kumaraa, N. S. Linge Gowda, K. Mantelingu, K. K. S. Rangappa, N-Bromosuccinimide assisted oxidation of tripeptides and their amino acid analogs: Synthesis, kinetics, and product studies, *J. Mol. Catal. A Chem*., **2009**, 309,172–177.
[24]. A. A. P. Khan, A. Khan, A. M. Asiri, N. Azum, M. A. Rub, Micro concentrations of Ru(III) used as homogenous catalyst in the oxidation of levothyroxine by N-bromosuccinimde and the mechanistic pathway, *J. Tai. Inst. Chem. Eng.*, **2014**, 1, 127–133.
[25]. B. Singh, L. Pandey, J. Sharma, S. M. Pandey, Mechanism of oxidation of some aliphatic ketones by N-bromosuccinimide in acidic media, *Tetrahedron.*,**1982**, 38(1), 169–172
[26]. Ashok Kumar Singh, Rajesh Kumar Singh, Jaya Srivastava, Rakesh Patel, ShahlaRahmani, Kinetics of Oxidation of Trehalose By Protonated N-Bromosuccinimide Using Rh (III) Chloride As Homogeneous Catalyst, *J Applicable Chem*., **2016**, 5(1), 204-218.
[27]. Ashok Kumar Singh, Priyanka Singh, Jaya Srivastava, Shahla Rahmani, Ravi Prakash, Rh(III)-Catalysis in The Kinetic Studies of Oxidation of D-Xylose by N-Bromosuccinimide in Acidic Medium, *J Applicable Chem*., **2015**, 4(5), 1507-1521.
[28]. M. Kalyana Chakravarthy, K. Ramakrishna, P. V.Subba Rao, Kinetics and Mechanism of Oxidation of Indigo Carmine with N-Bromosuccinimide-Effect of CTAB and SDS Micelles, *J Applicable Chem*., **2019**, 8(1), 403-411.
[29]. A. K. Singh, R. Negi, B. Jain, K. Yokraj, S. P. Singh, V. K. Sharma, Pd(II) Catalyzed Oxidative Degradation of Paracetamol by Chloramine-T in Acidic and Alkaline Media, *Ind. Eng. Chem. Res.*, **2011**, 50, 8407–8419.
[30]. K. N. Mohana, P. M. R. Bhandarkar, Oxidation of 2-Phenylethylamine with N-Bromosuccinimide in Acid and Alkaline Media: A Kinetic and Mechanistic Study, *J. Chinese Chem. Soc.*, **2007**, 54, 1223-1232.
[31]. M. G. Alder, J. E. Leffler, The Role of the Solvent in Radical Decomposition Reactions: Phenyl azo triphenylmethane, *J. Am. Chem. Soc.*,**1954**, 76, 1425–1427.
[32]. A. A. P. Khan, A. Mohd, S. Bano, K. S. Siddiqi, A. M. Asiri, Spectrophotometric methods for the determination of ampicillin by potassium permanganate and 1-chloro-2,4-dinitrobenzene in pharmaceuticals preparations, *Arab. J. Chem.*, **2015**, 8, 255–263.
[33]. P.F. Kruse, K. L. Grist, T. A. McCoy, Studies with N-halo reagents, *Anal. Chem.*, **1954**, 26 (8), 1319-1322.
[34]. C. Karunakaran, J. Ismail, S. M. Mannan, Acid catalysis in the N-Bromosuccnimide -propargyl alcohol reaction, *React. Kinet. Catal. Lett.*, **1994**, 53(1), 191–196.
[35]. K. N. Mohana, P. M. R. Bhandarkar, Mechanisitic investigation of oxidation of Metronidazole and Timidazole with N-Bromosuccinimide in acid medium: A Kinetic approach, *J. Iran. Chem. Soc.*, **2009**, 9(2), 277–287.
[36]. K. Ganapathy, C. Karunakaran, Kinetics and mechanism of oxidation of allyl alcohol by N-Bromosuccinimide, *Monatsh. Chem*., **1982**, 113, 1239–1244.
[37]. F. M. Chou, W. T. Wang, G. T. Wei,Using subcritical/supercritical fluid chromatography to separate acidic, basic and neutral compounds over an ionic liquid-functionalized stationary phase, *J.Chromatogr. A.*, **2009**, 1216, 3594–3599.
[38]. C. S. Reddy, P. S.Manjari, Homogeneous catalysis of oxovanadium(IV) in the oxidation of substituted 4-oxoacids by bromate in acid medium: A mechanistic study, *J Mol. Catal A: Chem.*, **2010**, 328, 76-87.
[39]. P. S. Manjari, C. S. Reddy, Aquachlororuthenium (III) catalysis in the oxidation of substituted 4-oxo-4-arylbutanoic acids by bromate in acid medium: a kinetic and mechanistic study and validity of linear free-energy relationships, *Trans. Met. Chem.*, **2011**, 36, 707-719.