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Oxidative cleavage of salbutamol with *N*-bromosuccinimide in acidic and alkaline media: A kinetic and mechanistic study

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Salbutamol sulfate (SBL) is a β_2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease (COPD). The kinetic study of oxidation of this bioactive compound is of much use in understanding the mechanistic profile in redox reactions. Consequently, the kinetics of oxidative degradation of SBL with *N*-bromosuccinimide (NBS) in $HClO_4$ and NaOH media has been studied at 308 K. The experimental rate laws obtained are $-d[NBS]/dt = [NBS][SBL]^x[H^+]^y$ in acidic medium and $-d[NBS]/dt = [NBS][SBL]^x[OH^-]$ in alkaline medium, where x and y are less than unity. The reactions were subjected to changes in concentration of succinimide, the reduction product of NBS, concentration of added neutral salt, dielectric permittivity and ionic strength of the medium. Solvent isotope effect has been studied using D_2O. The stoichiometry of the reaction has been determined and oxidation products were identified and characterized in both media. Activation parameters for the overall reactions have been computed from Arrhenius plot. $(Ch_2CO)_2\ N^+HBr$ and OBr^- have been postulated as the reactive oxidizing species in acidic and alkaline media, respectively. The oxidation reaction fails to induce polymerization of added acrylonitrile. It was found that the reaction was faster in alkaline medium in comparison with acidic medium. The observed results have been explained by plausible mechanisms and the relative rate laws have been deduced.

Key words: *N*-bromosuccinimide, salbutamol sulfate, oxidation kinetics, acidic and alkaline media.

INTRODUCTION

N-bromosuccinimide (NBS) is a source of positive halogen, and this reagent has been exploited as an oxidant for a variety of substrates [1–5] in both acidic and alkaline solutions. This potent oxidizing agent has been used in the determination of various pharmaceutical compounds [6–9]. However, a little information exists in the literature on oxidation kinetics of substrates particularly with respect to pharmaceuticals [10, 11], which may throw some light on the mechanism [12] of metabolic conversions in the biological system. In view of these facts, there is a considerable scope for the study of reactions with NBS to get better in sight of the speciation of NBS reaction models and to understand its redox chemistry in solutions.

Salbutamol sulfate (SBL) is a β_2-adrenergic receptor agonist used for the relief of bronchospasm in condition such as asthma and COPD. Salbutamol is a relevant medication for the treatment of asthma. It acts quickly on the nerves that control the airway muscles and causes them to relax and dilating the airways. It also relieves swelling of the airways that can be caused by the allergic response and helps to clear mucous that may contribute to asthmatic symptoms. SBL is specifically used for the following conditions such as acute asthma, certain conditions involving hyperkalemia. It is also used in obstetrics as a tocolytic to delay premature labor. It was therefore found to be of interest to investigate the mechanism of oxidation of this drug with *N*-bromosuccinimide. There was a need for understanding the oxidation mechanism of this drug, so that, the study could throw some light on the fate of the drug in the biological system.

In the light of available information and our continued interest on mechanistic studies on haloamiometric reactions in general and bioactive compounds in particular, the present investigation was undertaken. The present paper reports for the first time on the detailed kinetics of oxidation of SBL with NBS in $HClO_4$ and NaOH media. The work was carried out with a view to elucidate the mechanism of the reactions, put forward appropriate rate laws, identify the oxidation products of reactions, ascertain the reactive species of oxidant and compare the kinetic results and oxidative behaviour of NBS in acidic and alkaline solutions.

EXPERIMENTAL

Materials

An aqueous solution of NBS was prepared afresh

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each day from a G.R. Merck sample of the reagent, and its strength was checked by the iodo-metric method [13]. Analar grade SBL (Medrich, India) was used as received. All other reagents used were of analytical grade. Doubly distilled water was used throughout the investigations.

Kinetic measurements

All kinetic measurements were performed in glass stoppered pyrex boiling tubes coated black to eliminate photochemical effects. The reactions were carried out under pseudo-first-order conditions by taking a known excess of $[SBL]_o$ over $[NBS]_o$ at 308 K. Appropriate amounts of SBL, $HClO_4$ or NaOH solutions, mercuric acetate, sodium perchlorate, and water to keep the total volume constant were equilibrated at constant temperature (±0.1 deg). A measured amount of NBS solution also pre-equilibrated at the same temperature was rapidly added to the mixture. The progress of the reaction was monitored by estimating the amount of unconsumed NBS at regular time intervals iodometrically. The course of reaction was studied for atleast two half-lives. The pseudo-first-order rate constants (k_{obs}) calculated from the linear plots of log[NBS] *vs*. time were reproducible within ±4%. Regression analysis of the experimental data to obtain regression coefficient, *r*, was performed using MS Excel.

Stoichiometry and product analysis

Reaction mixtures containing varying ratios of NBS and SBL in presence of 0.1 $mol{\cdot}dm^{-3}$ $HClO_4$ or 0.01 $mol{\cdot}dm^{-3}$ NaOH at 308 K were kept aside for 48 h, so that the substrate was completely converted into products. Estimation of the unreacted NBS showed that one mole of substrate utilized one mole of oxidant in both acidic and alkaline media, confirming the following stoichiometry:

$$C_{13}H_{21}O_3N + RNBr + H_2O \rightarrow C_8H_8O_3 + + HCHO + C_4H_{11}N + RNH + HBr \qquad (1)$$

$$C_{13}H_{21}O_3N + RNBrv \rightarrow C_8H_8O_3 + + C_5H_{11}N + RNH + HBr \qquad (2)$$

where $R = (CH_2CO)_2$.

The reaction products were neutralized with acid/alkali and extracted with ether. The combined ether extract was evaporated and subjected to column chromatography on silica gel using gradient elution (chloroform). The reduction product of NBS, succinimide (RNH) was detected by spot tests [14] and confirmed by IR absorption bands. The oxidation products of SBL were found to be 3-hydroxy-4-(hydroxymethyl)benzaldehyde, formaldehyde and *t*-butyl amine in acidic medium, and 3-hydroxy-4-(hydroxymethyl)benzaldehyde, methylene-*N*-*t*-butylamine in the case of alkaline medium and were detected by spot tests [14]. 3-hydroxy-4-(hydroxymethyl)benzaldehyde was further confirmed by IR absorption bands. RNH: a broad band at 3450 cm^{-1} for NH stretching mode and a sharp band at 1698 cm^{-1} for C=O stretching mode. 3-hydroxy-4-(hydroxymethyl)benzaldehyde: 1705 cm^{-1} (C=O stretch), 2848 cm^{-1} (aldehydic C–H stretch) and 3473 cm^{-1} (O–H stretch).

RESULTS

The kinetics of oxidation of SBL with NBS has been kinetically investigated at different initial concentrations of reactants in the presence of $HClO_4$ or NaOH at 308 K. In the present investigations we could not establish the identical experimental conditions for acidic and alkaline media. The salient features obtained in these two media are discussed separately.

Kinetics of oxidation in acidic medium

Under pseudo-first-order conditions ([SBL] >> [NBS]) at constant $[HClO_4]$ and temperature, plots of log[NBS] *vs*. time were linear ($r \geq 0.996$) indicating a first-order dependence of rate on $[NBS]_o$. The pseudo-first-order rate constant (k_{obs}) calculated is given in Table 1. Further, the values of k_{obs} calculated from these plots are unaltered with variation of $[NBS]_o$ confirming the first-order dependence on $[NBS]_o$.

Table 1. Effect of varying concentrations of oxidant, substrate and $HClO_4$ on the reaction rate at 308 K; $[Hg(OAC)_2] = 1{\times}10^{-3}$ $mol{\cdot}dm^{-3}$; $\mu = 0.2$ $mol{\cdot}dm^{-3}$.

$[NBS]{\times}10^4$ ($mol{\cdot}dm^{-3}$)	$[SBL]{\times}10^3$ ($mol{\cdot}dm^{-3}$)	$[HClO_4]{\times}10$ ($mol{\cdot}dm^{-3}$)	$k_{obs}{\times}10^4$ (s^{-1})
1.0	8.0	1.0	3.30 ± 0.0351
3.0	8.0	1.0	3.37 ± 0.0350
5.0	8.0	1.0	3.36 ± 0.0450
7.0	8.0	1.0	3.31 ± 0.0458
9.0	8.0	1.0	3.38 ± 0.0503
5.0	4.0	1.0	2.20 ± 0.0405
5.0	6.0	1.0	2.90 ± 0.0350
5.0	10.0	1.0	3.99 ± 0.0360
5.0	12.0	1.0	4.36 ± 0.0362
5.0	8.0	0.6	2.29 ± 0.0430
5.0	8.0	0.8	2.88 ± 0.0356
5.0	8.0	1.2	3.99 ± 0.0358
5.0	8.0	1.4	4.46 ± 0.0430
5.0 [a]	8.0	1.0	3.34 ± 0.0442
5.0 [b]	8.0	1.0	3.37 ± 0.0353

[a] $\mu = 0.25$ $mol{\cdot}dm^{-3}$; [b] $\mu = 0.3$ $mol{\cdot}dm^{-3}$.

The rate increased with increase in $[SBL]_o$ (Table 1). A plot of logk_{obs} *vs*. log[SBL] was linear (Fig. 1; $r = 0.998$) with a slope of 0.62 indicating fractional order dependence of the rate on $[SBL]_o$. The rate increased with increase in [$HClO_4$] (Table 1) and a plot of logk_{obs} *vs*. log[$HClO_4$] was linear (Fig. 2; r = 0.999) with a slope of 0.78 indicating fractional order with respect to [H^+]. At constant [H^+], addition of chloride ions in the form of NaCl does not change the rate of reaction.

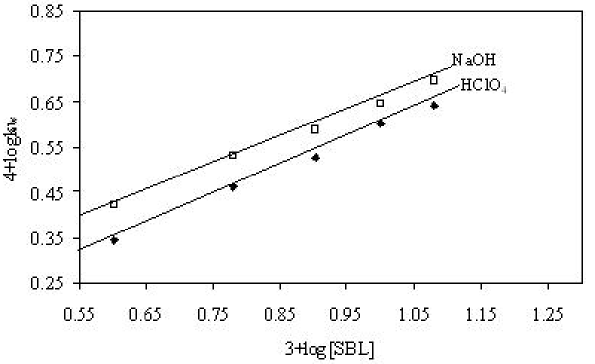


Fig. 1. Plot of 4 + logk_{obs} *vs*. 3 + log[SBL].

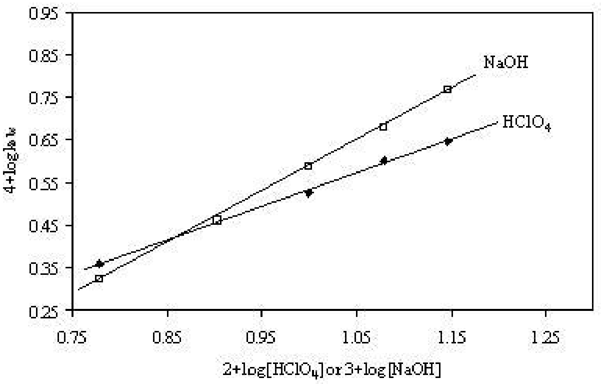


Fig. 2. Plot of 2 + log[$HClO_4$] or 3 + log[NaOH] *vs*. 4 + logk_{obs}.

Addition of succinimide (0.0002–0.001 mol·dm^{-3}) to the reaction mixture, variation of ionic strength of the medium (0.2–0.3 mol·dm^{-3}) and addition of mercuric acetate (0.001–0.005 mol·dm^{-3}) had no significant effect on the rate. The rate increased with increasing CH_3CN content (0–20% v/v) and the results are shown in Table 2.

Table 2. Effect of varying dielectric permittivity of the medium on the reaction rate at 308 K.

CH_3CN (% v/v)	D	$k_{obs}\times10^4$ (s^{-1})	
		Acidic[a]	Alkaline[b]
0	73.6	3.36 ± 0.0450	3.87 ± 0.0340
5	71.8	4.38 ± 0.0501	3.48 ± 0.0355
10	70.0	6.06 ± 0.0525	2.88 ± 0.0345
15	68.2	7.79 ± 0.0460	2.51 ± 0.0430
20	66.5	10.28 ± 0.0380	2.14 ± 0.0501

[a] [NBS] = 5×10^{-4} mol·dm^{-3}; [SBL] = 8×10^{-3} mol·dm^{-3}; [$HClO_4$] = 0.1 mol·dm^{-3}; μ = 0.2 mol·dm^{-3}; [$Hg(OAC)_2$] = 1×10^{-3} mol·dm^{-3};
[b] [NBS]= 5×10^{-4} mol·dm^{-3}; [SBL] = 8×10^{-3} mol·dm^{-3}; [NaOH] = 1×10^{-2} mol·dm^{-3}; μ = 0.1 mol·dm^{-3}; [$Hg(OAC)_2$] = 1×10^{-3} mol·dm^{-3}.

Plot of logk_{obs} *vs*. 1/D was linear (r = 0.998) with a positive slope. The values of permittivity (D) for CH_3CN–H_2O mixtures are calculated from the equation $D = D_wV_w + D_AV_A$ where D_w and D_A are the dielectric permittivities of pure water and acetonitrile and V_w and V_A are the volume fractions of components, water and acetonitrile in the total mixture. Blank experiments performed indicated that CH_3CN was not oxidized with NBS under the experimental conditions employed. Solvent isotope study in D_2O medium was made. The value of $k_{obs}(H_2O)$ is 3.36 and that of $k_{obs}(D_2O)$ is 2.40 leading to solvent isotope effect of $k_{obs}(H_2O)/k_{obs}(D_2O)$ = 1.40. Proton inventory studies were made in H_2O–D_2O mixtures and the results are shown in Table 3. The corresponding proton inventory plot for the rate constant k_{obs} in a solvent mixture containing deuterium atom fraction (n) is given in Fig. 3.

Table 3. Proton inventory studies in H_2O-D_2O mixture at 308 K

Atom fraction of D_2O (n)	$k_{obs}\times10^4$ (s^{-1})	
	Acidic[a]	Alkaline[b]
0.0	3.36 ± 0.0450	3.87 ± 0.0340
0.25	3.19 ± 0.0353	3.37 ± 0.0405
0.50	2.98 ± 0.0424	3.03 ± 0.0371
0.75	2.70 ± 0.0503	2.80 ± 0.0455
0.95	2.40 ± 0.0362	2.30 ± 0.0358

[a] [NBS] = 5×10^{-4} mol·dm^{-3}; [SBL] = 8×10^{-3} mol·dm^{-3}; [$HClO_4$] = 0.1 mol·dm^{-3}; μ = 0.2 mol·dm^{-3}; [$Hg(OAC)_2$] = 1×10^{-3} mol·dm^{-3};
[b] [NBS] = 5×10^{-4} mol·dm^{-3}; [SBL] = 8×10^{-3} mol·dm^{-3}; [NaOH] = 1×10^{-2} mol·dm^{-3}; μ = 0.1 mol·dm^{-3}; [$Hg(OAC)_2$] = 1×10^{-3} mol·dm^{-3}.

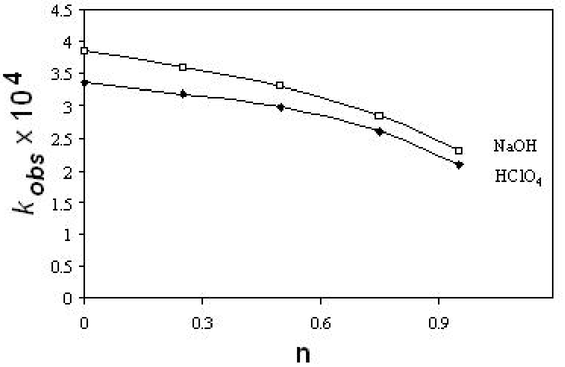


Fig. 3. Plot of k_{obs} *vs*. n.

The reaction was studied at different temperatures (300–318 K) keeping other experimental conditions constant. From the linear Arrhenius plot of logk_{obs} *vs*. 1/T (Fig. 4; r = 0.999), the values of activation parameters for the overall reaction were computed. The results are compiled in Table 4. The absence of free radicals during the course of oxidation was confirmed when no polymerization was initiated with addition of acrylonitrile solution to the reaction mixture.

Kinetics of oxidation in alkaline medium

With substrate in excess at constant [NaOH] and temperature, the $[NBS]_o$ was varied. Plots of log[NBS] *vs*. time were linear ($r \geq 0.998$) indicating a first-order dependence of the rate on $[NBS]_o$. The pseudo-first-order rate constant (k_{obs}) obtained is listed in Table 5. The values of k_{obs} increased with increase in [SBL] (Table 5) and a plot of $\log k_{nobs}$ *vs*. log[SBL] (Fig. 1; $r = 0.999$) gave a slope of 0.58 indicating fractional-order dependence of the rate on $[SBL]_o$. The higher[NaOH], i.e.$[OH^-]$ leads to higher k_{obs} (Table 5) and from the linear plot of $\log k_{obs}$ *vs*. log[NaOH], (Fig. 2; $r = 0.996$) an order of 1.02 was obtained showing first-order dependence of the rate on [NaOH].

Table 4. Effect of varying temperature on the reaction rate and activation parameters for the oxidation of SBL.

Temperature (K)	$k_{obs}\times10^4$ (s^{-1})	
	Acidic[a]	Alkaline[b]
300	1.38 ± 0.0475	1.90 ± 0.0370
304	2.18 ± 0.0510	2.69 ± 0.0358
308	3.36 ± 0.0450	3.87 ± 0.0340
313	6.45 ± 0.0550	5.45 ± 0.0430
318	11.49 ± 0.0515	8.51 ± 0.0425
E_a ($kJ\cdot mol^{-1}$)	94.54	66.07
$\Delta H^{\neq}$ ($kJ\cdot mol^{-1}$)	91.97	63.51
$\Delta G^{\neq}$ ($kJ\cdot mol^{-1}$)	95.86	95.72
$\Delta S^{\neq}$ ($JK^{-1}\cdot mol^{-1}$)	–12.60	–104.36

[a] $[NBS] = 5\times10^{-4}$ $mol\cdot dm^{-3}$; $[SBL] = 8\times10^{-3}$ $mol\cdot dm^{-3}$; $[HClO_4] = 0.1$ $mol\cdot dm^{-3}$; $\mu = 0.2$ $mol\cdot dm^{-3}$; $[Hg(OAC)_2] = 1\times10^{-3}$ $mol\cdot dm^{-3}$;
[b] $[NBS] = 5\times10^{-4}$ $mol\cdot dm^{-3}$; $[SBL] = 8\times10^{-3}$ $mol\cdot dm^{-3}$; $[NaOH] = 1\times10^{-2}$ $mol\cdot dm^{-3}$; $\mu = 0.1$ $mol\cdot dm^{-3}$; $[Hg(OAC)_2] = 1\times10^{-3}$ $mol\cdot dm^{-3}$.

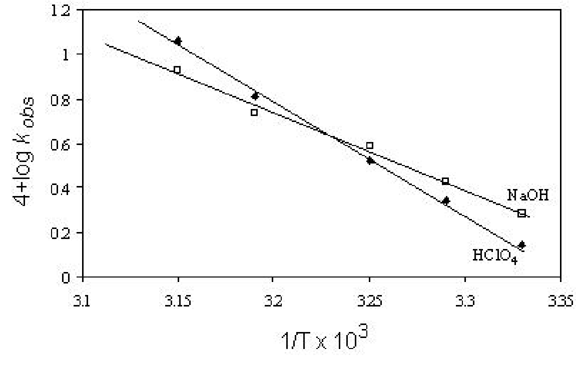


Fig. 4. Arrhenius plot of 4 + $\log k_{obs}$ *vs*. $10^3/T$.

Addition of succinimide (0.0002–0.001 $mol\cdot dm^{-3}$) to the reaction mixture, variation of ionic strength of the medium (0.1–0.3 $mol\cdot dm^{-3}$) and addition of mercuric acetate (0.001–0.005 $mol\cdot dm^{-3}$) had no significant effect on the rate. The rate decreased with increasing CH_3CN content (0–20% v/v) and the results are shown in Table 2. Plot of $\log k_{obs}$ *vs*. $1/D$ was linear ($r = 0.998$) with a negative slope. Solvent isotope study in D_2O medium was made. The value of $k_{obs}(H_2O)$ is 3.87 and that of $k_{obs}(D_2O)$ is 2.30 leading to solvent isotope effect $k_{obs}(H_2O)/k_{obs}(D_2O) = 1.68$. Proton inventory studies were made in H_2O-D_2O mixtures, and the results are shown in Table 3. The corresponding proton inventory plot for the rate constant k_{obs} in a solvent mixture containing deuterium atom fraction (*n*) is given in Fig. 3. Kinetic and thermodynamic parameters were calculated by studying the reaction at different temperatures (300–318 K) and from the linear Arrhenius plot of $\log k_{obs}$ *vs*. $1/T$. (Fig. 4; $r = 0.999$). These results are given in Table 4. Absence of free radicals in the reaction mixture has been demonstrated by the acrylonitrile test.

Table 5. Effect of varying concentrations of oxidant, substrate and NaOH on the reaction rate at 308 K; $[Hg(OAC)_2] = 1\times10^{-3}$ $mol\cdot dm^{-3}$; $\mu = 0.1$ $mol\cdot dm^{-3}$.

$[NBS]\times10^4$ ($mol\cdot dm^{-3}$)	$[SBL]\times10^3$ ($mol\cdot dm^{-3}$)	$[NaOH]\times10^2$ ($mol\cdot dm^{-3}$)	$k_{obs}\times10^4$ (s^{-1})
1.0	8.0	1.0	3.86 ± 0.0355
3.0	8.0	1.0	3.89 ± 0.0351
5.0	8.0	1.0	3.87 ± 0.0340
7.0	8.0	1.0	3.81 ± 0.0360
9.0	8.0	1.0	3.80 ± 0.0470
5.0	4.0	1.0	2.64 ± 0.0503
5.0	6.0	1.0	3.38 ± 0.0458
5.0	10.0	1.0	4.41 ± 0.0430
5.0	12.0	1.0	4.95 ± 0.0356
5.0	8.0	0.6	2.10 ± 0.0442
5.0	8.0	0.8	2.88 ± 0.0353
5.0	8.0	1.2	4.78 ± 0.0503
5.0	8.0	1.4	5.87 ± 0.0358
[a]5.0	8.0	1.0	3.82 ± 0.0362
[b]5.0	8.0	1.0	3.85 ± 0.0405

[a] $\mu = 0.15$ $mol\cdot dm^{-3}$; [b] $\mu = 0.2$ $mol\cdot dm^{-3}$.

DISCUSSION AND MECHANISMS

Reactive species of NBS

NBS is a double equivalent oxidant which oxidizes many substrates through NBS itself or Br^+ or RN^+HBr or hypobromite anion. The reactive species responsible for the oxidizing character may depend on the pH of the medium [3]. Depending on the pH of the medium, NBS furnishes different types of reactive species in solutions [15–17] as shown in the following equations:

$$RNBr + H^+ \leftrightarrows RN^+HBr \qquad (3)$$

$$RNBr + H_2O \leftrightarrows RNH + HOBr \qquad (4)$$

$$HOBr + OH^- \leftrightarrows OBr^- + H_2O \qquad (5)$$

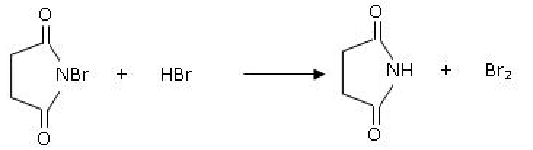
$$RNBr + H^+ \leftrightarrows RNH + Br^+ \qquad (6)$$

$$Br^+ + H_2O \leftrightarrows (H_2OBr)^+ \qquad (7)$$

$$RNBr + OH^- \leftrightarrows RNH + OBr^- \qquad (8)$$

where $R = (CH_2CO)_2$.

In acidic medium, the probable reactive species of NBS are NBS itself or Br^+ or protonated NBS (RN^+HBr), and the reactive species in alkaline solutions are NBS itself or HOBr or OBr^-. It may be pointed out that, all kinetic studies have been made in presence of mercury(II) acetate in order to avoid any possible bromine oxidation which may be produced as follows:



(9)

Mercuric acetate acts as a capture agent for any Br^- formed in the reaction and exists as $HgBr_4^{2-}$ or unionized $HgBr_2$ and ensures that oxidation takes place purely through NBS [18, 19].

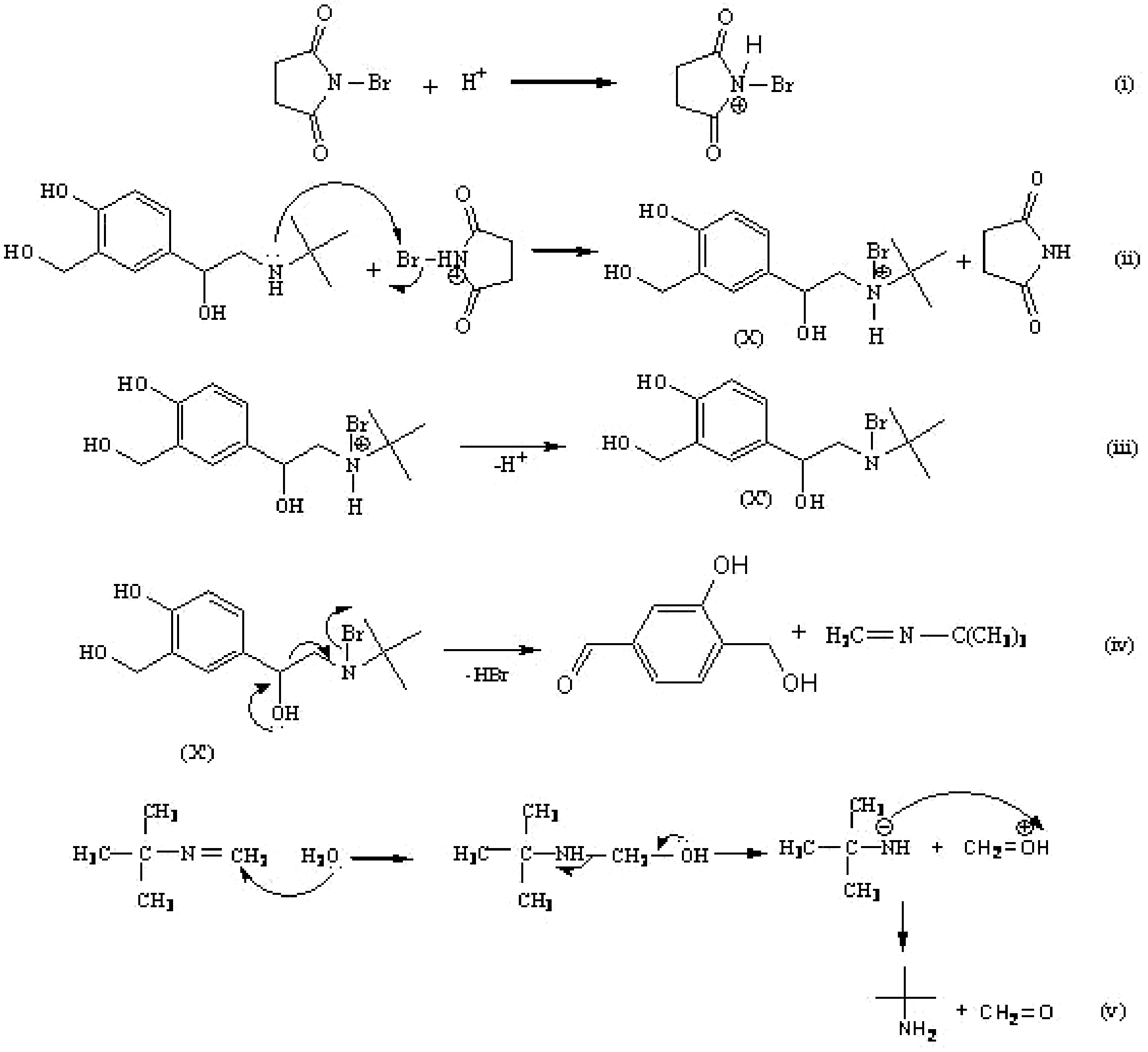
Mechanism and rate law in acidic medium

Most investigations of NBS oxidations of organic substrates have assumed that, the molecular NBS acts only through its positive polar end [20, 21]. In the present investigation, acceleration of the rate by increasing concentration of H^+, assumes that protonated species of NBS, i.e., RN^+HBr is the most likely oxidizing species. Further, the insignificant effect of initially added product succinimide, (RNH) allows us to take RN^+HBr as the active oxidizing species. The protonated NBS reacts with SBL to form a complex which further undergo hydrolysis and intramolecular rearrangement to form products.

$$\begin{array}{llll} RNBr + H^+ & \overset{K_1}{\rightleftharpoons} RN^+HBr & \text{fast} & \text{(i)} \\ RN^+HBr + SBL & \overset{K_2}{\rightleftharpoons} X & \text{fast} & \text{(ii)} \\ X & \xrightarrow{k_3} X' & \text{slow and rds} & \text{(iii)} \\ X' + H_2O & \xrightarrow{k_4} \text{Products} & \text{fast} & \text{(iv)} \end{array}$$

Scheme 1.

In Scheme 1, X and X′ are the intermediate species whose structures are shown in Scheme 2, where a detailed mechanistic interpretation of SBL oxidation with NBS in acid medium is proposed.



Scheme 2.

Step (iii) of Scheme 1 determines the overall rate:

$$rate = \frac{-d[RNBr]}{dt} = k_3[X]. \qquad (10)$$

If $[RNBr]_t$ represents the total effective concentration of NBS in solution, then

$$[RNBr]_t = [RNBr] + [RN^+HBr] + [X] \qquad (11)$$

From step (i) of Scheme 1

$$[RNBr] = [RN^+HBr]/K_1[H^+] \qquad (12)$$

From step (ii) of Scheme 1

$$[RN^+HBr] = [X]/K_2[SBL] \qquad (13)$$

Substituting Eqns. (12) and (13) in Eqn. (11) one obtains:

$$[X] = \frac{K_1K_2[RNBr]_t[SBL][H^+]}{1+K_1[H^+]+K_1K_2[SBL][H^+]} \qquad (14)$$

By substituting for [X] from Eqn. (14) in Eqn. (10), the following rate law can be obtained:

$$rate = \frac{K_1K_2k_3[RNBr]_t[SBL][H^+]}{1+K_1[H^+]+K_1K_2[SBL][H^+]} \qquad (15)$$

Since *rate* = $k_{obs}[RNBr]_t$, Eqn. (15) can be transformed into Eqns. (16) and (17):

$$k_{obs} = \frac{K_1K_2k_3[SBL][H^+]}{1+K_1[H^+][1+K_2[SBL]} \qquad (16)$$

$$\frac{1}{k_{obs}} = \frac{1}{K_1K_2k_3[SBL][H^+]} + \frac{1}{K_2k_3[SBL]} + \frac{1}{k_3}$$

$$\frac{1}{k_{obs}} = \frac{1}{K_2k_3[SBL]}\left\{\frac{1}{K_1[H^+]}+1\right\} + \frac{1}{k_3} \qquad (17)$$

Based on Eqn. (17), plot of $1/k_{obs}$ *vs.* 1/[SBL] (Fig. 5; $r = 0.998$) at constant $[H^+]$ and temperature has been found to be linear. From the intercept of the above plot, the value of k_3 was found to be 7.64×10^{-4} s^{-1}.

The change in solvent composition by varying the CH_3CN content in CH_3CN-H_2O affects the reaction rate. For limiting case of zero angle of approach between two dipoles or an ion-dipole system, Amis [22] has shown that a plot of $\log k_{obs}$ *vs.* $1/D$ gives a straight line, with a positive slope for a reaction involving a positive ion and a dipole and a negative slope for a negative ion-dipole or dipole-dipole interactions. In the present investigation a plot of $\log k_{obs}$ *vs.* $1/D$ was linear with a positive slope. This observation indicates the ion-dipole nature of the rate determining step in the reaction sequence and also points to extending of charge to the transition state.

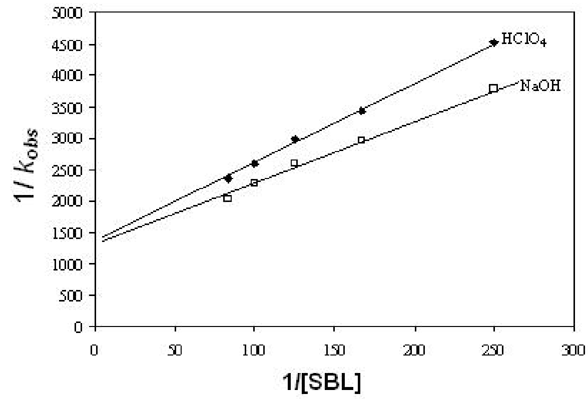


Fig. 5. Plot of $1/k_{obs}$ *vs.* 1/[SBL].

The observed solvent isotope effect supports the proposed mechanism and the derived rate law. For a reaction involving a fast equilibrium H^+ or OH^- ion transfer, the rate increases in D_2O medium, since D_3O^+ and OD^- are stronger acid and stronger base respectively than H_3O^+ and OH^- ions [23, 24]. In the present case, the observed solvent isotope effect of $k_{obs}(H_2O)/k_{obs}(D_2O) > 1$ is due to the protonation step followed by hydrolysis involving the OH bond scission. The retardation of rate in D_2O is due to the hydrolysis step which tends to make the normal kinetic isotope effect. The proton inventory studies made in H_2O-D_2O mixture could throw light on the nature of the transition state. The dependence of the rate constant, k_{obs} on the deuterium atom fraction 'n' in the solvent mixture is given by the following form of Gross-Butler equation [25]:

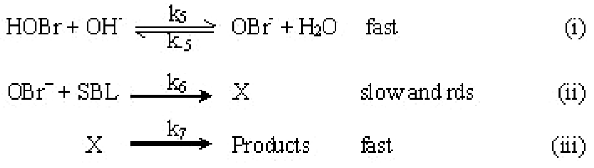
$$\frac{k_o'}{k_n'} = \frac{\pi TS(1-n+n\varphi_i)}{\pi RS(1-n+n\varphi_j)} \qquad (18)$$

where ϕ_i and ϕ_j are isotope fractionation factor for isotopically exchangeable hydrogen sites in the transition state (TS) and in the ground/reactant state (RS), respectively. The Gross-Butler equation permits the evaluation of ϕ_i when the value of ϕ_j is known. However, the curvature of proton inventory plot could reflect the number of exchangeable proton in the reaction [25]. Plot of k_{obs} versus n is a curve in the present case, and this, in comparison with the standard curves, indicate the involvement of a single proton or H-D exchange in the reaction sequence [26]. This proton exchange is indicative of the participation of hydrogen in the formation of transition state.

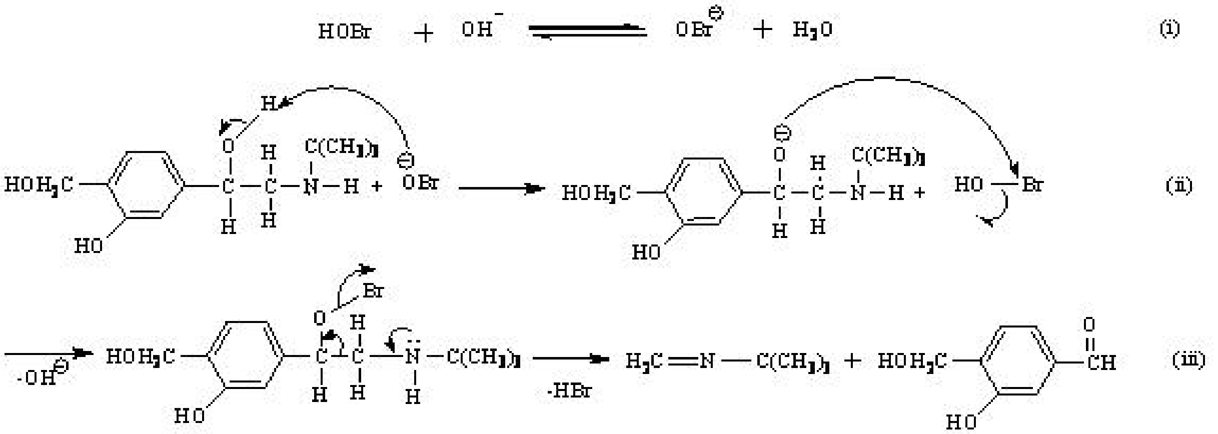
The negligible influence of added succinimide and halide ions on the rate are in agreement with the proposed mechanism. The proposed mechanism is also supported by the high values of energy of activation and other thermodynamic parameters. The fairly high positive value of $\Delta H^{\neq}$ indicates that, the transition state is highly solvated.

Mechanism and rate law in alkaline medium

NBS is a double equivalent oxidant, which oxidizes many substrate through NBS itself, or hypobromite anion [27, 28]. The reaction exhibits 1:2 stoichiometry of SBL and NBS with unit order dependence on [NBS]. Increase in rate with increasing $[OH^-]$ can be well explained [29] by the formation of oxidant species OBr^- according to the equilibria (5) and (8). Insignificant effect of added succinimide on the rate can be attributed to the involvement of OBr^- according to the equilibrium step (5). Hence OBr^- reacts with the substrate to form a complex (X) in the rate determining step, which then undergoes decomposition in the fast step to give products as shown in Scheme 3. A detailed mechanistic interpretation is shown in Scheme 4.



Scheme 3.



Scheme 4.

From the slow step of Scheme 3

$$rate = \frac{-d[RNBr]}{dt} = k_6[OBr^-][SBL] \qquad (19)$$

Applying steady state condition for OBr^-, it can be shown that

$$[OBr^-] = \frac{k_5[HOBr][OH^-]}{k_{-5}[H_2O] + k_6[SBL]} \qquad (20)$$

On substituting Eqn. (20) in Eqn. (19), the following rate law (Eqn. (21)) is obtained:

$$rate = \frac{k_5k_6[HOBr][OH^-][SBL]}{k_{-5}[H_2O] + k_6[SBL]} \qquad (21)$$

Since $rate = k_{obs}[NBS]$, Eqn. (21) can be transferred into Eqns. (22) and (23):

$$k_{obs} = \frac{k_5k_6[OH^-][SBL]}{k_{-5}[H_2O] + k_6[SBL]} \qquad (22)$$

$$\frac{1}{k_{obs}} = \frac{k_{-5}[H_2O]}{k_5k_6[OH^-][SBL]} + \frac{1}{k_5[OH^-]} \qquad (23)$$

Based on Eqn. (23), a plot of $1/k_{obs}$ *vs* 1/[SBL] (Fig. 5, $r = 0.997$) at constant $[OH^-]$ and temperature has been found to be linear. From the slope and intercept of the above plot, the values of k_5 and k_{-5}/k_6 were found to be 0.0816 $mol^{-1}\cdot dm^3\cdot s^{-1}$ and 1.513×10^{-4} respectively, with $[H_2O] = 55.5$ $mol\cdot dm^{-3}$. The proposed Scheme 3 and rate law (Eqn. (21)) are also substantiated by the experimental results discussed below.

The negligible influence of the added succinimide and variation of ionic strength of the medium is consistent with the proposed mechanism. The dielectric effect observed in the present case indicates ion-dipole interaction in the rate limiting step. The sign and magnitude of $\Delta S^{\neq}$ observed suggested that the activated complex is more compact than the ground state. The positive free energy of activation shows that the transition state is highly solvated.

The solvent isotope effect $k_{obs}(H_2O)/k_{obs}(D_2O) > 1$ is noticed in alkaline medium supports the proposed mechanism. The magnitude of retardation in D_2O medium can be attributed to the first-order dependence on [OH$^-$] and may be due to the involvement of hydrolysis step in the rate limiting step.

CONCLUSIONS

In conclusion, the stoichiometry of oxidation of salbutamol with NBS is same in both acidic and alkaline media. Kinetic studies in acidic medium reveal that, $(CH_2CO)_2N^+HBr$ as active oxidant species which oxidizes the substrate to the corresponding aldehyde. In alkaline medium the reaction takes place between the substrate and OBr^- to form the corresponding aldehyde. The magnitude of the two activation energies indicates that, the reaction is faster in alkaline medium compared to acidic medium. The different active oxidizing species involved in the two media are responsible for the difference in activity. Hence, the kinetics of oxidation of SBL with NBS is more facile in alkaline medium in comparison with acidic medium.

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ИЗСЛЕДВАНЕ НА КИНЕТИКАТА И МЕХАНИЗМА НА ОКИСЛИТЕЛНО РАЗПАДАНЕ НА САЛБУТАМОЛ С *N*-БРОМСУКЦИНАМИД В КИСЕЛА И АЛКАЛНА СРЕДА

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(Резюме)

Салбутамол сулфат (SBL) е β_2-адренергичен рецептор агонист използван за облекчаване на бронхоспазми при астма и хронична обструктивна белодробна болест (COPD). Кинетичното изследване на окислението на това биологично активно съединение се използва за изясняване на механизма на редокс реакции. Затова кинетиката на окислително разлагане на SBL с *N*-бромсуцинимид (NBS) в среда от $HClO_4$ или NaOH е изследвано при 308 K. Експериментално получените уравнения за скоростта са $-d[\mathrm{NBS}]/dt = [\mathrm{NBS}][\mathrm{SBL}]^x[\mathrm{H}^+]^y$ в кисела среда и $-d[\mathrm{NBS}]/dt = [\mathrm{NBS}][\mathrm{SBL}]^x[\mathrm{OH}^-]$ в алкална среда, където x и y са по-малки от единица. Реакциите са провеждани при промени в концентрацията на суцинимид, продукта на редукция на NBS, концентрацията на добавените неутрални соли, диелектричната проводимост и йонната сила на средата. Изотопния ефект на разтворителя е изследван като е използвана D_2O. Определена е стехиометрията на реакцията и са идентифицирани и охарактеризирани продуктите на окисление в двете среди. Параметрите на активация за сумарните реакции са изчислени от Арениусовите зависимости. Като реакционни окислителни форми са приети $(Ch_2CO)_2N^+HBr$ и OBr^- съответно в кисела или алкална среда. Реакцията на окисление не води до полимеризация на добавен акрилонитрил. Намерено е, че реакцията е по-бърза в алкална среда отколкото в кисела среда. Предложени са механизми за обяснение на получените резултати и съответни уравнения за скоростта на рекциите.