

Mechanistic Investigation of Oxidation of Metronidazole and Tinidazole with *N*-Bromosuccinimide in Acid Medium: A Kinetic Approach

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Metronidazole (MTZ) and tinidazole (TNZ) belong to nitroimidazole group of drugs used to treat infections such as amoebiasis, giardiasis and trichomoniasis. The kinetics of oxidation of MTZ and TNZ with *N*-bromosuccinimide (NBS) in perchloric acid medium has been investigated at 308 K. A 1:1 stoichiometry has been observed in both MTZ and TNZ cases. The oxidation reactions of both MTZ and TNZ follow the same rate law, $-d[\text{NBS}]/dt = [\text{NBS}][\text{Sub}][\text{H}^+]$. However, in case of MTZ, at higher concentrations of H^+ (0.006-0.01 mol dm⁻³), the rate law obtained is $-d[\text{NBS}]/dt = [\text{NBS}][\text{MTZ}][\text{H}^+]^{-1}$. Accelerating effect of $[\text{Cl}^-]$ and retardation of the added succinimide on the reaction rate have been observed in the case of MTZ. The reactions were examined with reference to changes in concentration of added neutral salt, ionic strength and dielectric permittivity of the medium. The overall activation parameters have been evaluated from the Arrhenius plot. The reactive oxidizing species of NBS have been determined. The main oxidation products were identified by IR and ¹H NMR spectral analyses. The observed results have been explained by plausible mechanisms and the relative rate laws have been deduced.

Keywords: Oxidation kinetics, Metronidazole, Tinidazole, *N*-Bromosuccinimide, Acid medium

INTRODUCTION

Oxidative degradation of bio-active compounds is one of the well-documented biochemical processes. However, the exact mechanism of the metabolic conversion of medicinal compounds is not well understood, and remains an area for further experimentation. Metronidazole (2-methyl-5-nitro-1-imidazole ethanol) and tinidazole [1-(2-ethylsulfonylethyl)-2-methyl-5-nitro imidazole] are anti-bacterial and anti-protozoal drugs. They are commonly used to treat a condition called amoebiasis [1-2]. MTZ and TNZ are drugs of choice for the treatment of giardiasis, anaerobic bacterial infection, bacterial vaginosis, and antibiotic associated pseudomembranous colitis, the most frequent side effect of nausea. The activity is totally

dependent on the organisms and system of an anaerobic energy production. In the presence of an anaerobic electron transport system, the nitrogen group of these compounds is reduced to a series of transiently produced reactive intermediates that are thought to cause DNA damage. Although the unique redox system of anaerobes accounts for the selective antibacterial activities of MTZ and TNZ, these compounds are also mutagen and radiosensitizers of hypoxic mammalian cells.

N-Bromosuccinimide (NBS) is a source of positive halogen, and this reagent has been exploited as an oxidant for a variety of substrates in both acidic and alkaline solutions [3-7]. The use of NBS as an oxidant is extensive in the determination of number of pharmaceutical compounds [8-11]. However, a little information exists in the literature on NBS reactions, particularly with respect to the oxidation

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kinetics of pharmaceuticals [12,13], which may throw some light on the mechanism [1] of metabolic conversions in biological systems. In view of these facts, there is a considerable scope for the study of reactions with NBS to get better insight of the speciation of NBS reaction models and to understand its redox chemistry in solutions. The present paper reports for the first time on the detailed kinetics of oxidation of MTZ and TNZ with NBS in HClO₄ medium. The work was carried out with a view to elucidate the mechanisms of the reactions, put forward appropriate rate laws, identify the oxidation products of reactions and ascertain the reactive species of oxidant.

EXPERIMENTAL

Materials

An aqueous solution of NBS was prepared afresh each day from a G.R. Merck sample of the reagent and its strength was checked by the iodometric method. Pharmaceutical grade metronidazole and tinidazole (supplied by Cipla India Limited, Mumbai, India) were used as received. All other reagents, namely perchloric acid, sodium perchlorate, mercuric acetate and succinimide were of Analar grade. Doubly distilled water was used throughout the investigations.

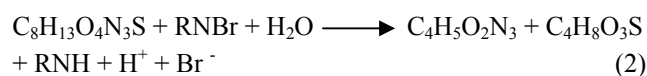
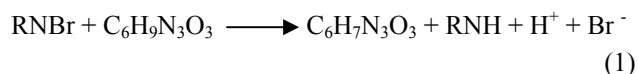
Kinetic Measurements

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 [MTZ]₀/[TNZ]₀ over [NBS]₀ at 308 K. Appropriate amounts of MTZ/TNZ, HClO₄ solutions, mercuric acetate, sodium perchlorate and water to keep the total volume constant were equilibrated at constant temperature (±0.1 °C). 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 at least 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 the regression co-efficient, *r* was performed using MS-Excel

program.

Stoichiometry and Product Analysis

Reaction mixtures containing varying ratios of NBS and MTZ/TNZ in the presence of HClO₄ at 308 K were kept aside for 48 h, so that the substrates were completely converted into products. Estimation of the unreacted NBS showed that, one mole of substrate consumed one mole of oxidant in both cases. The observed stoichiometry for MTZ and TNZ can be represented by the Eqs. (1) and (2), respectively.



where R is (CH₂CO)₂.

Succinimide (RNH), as the reduction product of NBS, was detected by the method reported elsewhere [14]. Further, the presence of RNH was confirmed by IR absorption bands; a broad band at around 3450 cm⁻¹ for N-H stretching mode, and a sharp band at 1698 cm⁻¹ for C=O stretching mode were observed. The oxidation product of MTZ was found to be 2-methyl-5-nitro-1-imidazole ethanal which was detected by conventional spot tests [15] and also by the 2,4-DNP derivative. Furthermore, the presence of aldehyde was confirmed by its IR absorption bands at 1720 cm⁻¹ for C=O stretching and at 2852 cm⁻¹ for aldehydic C-H stretching modes. The IR spectra were recorded on JASCO FT-IR spectrometer using KBr pellets.

The oxidation products of TNZ were extracted several times with diethyl ether, evaporated and separated by column chromatography. After initial separation, the products were detected by conventional spot tests [15], and identified as 2-methyl-5-nitro-1H-imidazole (Y) and 2-ethyl sulphonyl acetaldehyde (Z) by its ¹H NMR spectral studies. Y (D₂O): δ 2.4 (s, 3H, CH₃), 7.9 (s, H, Ar-H), 13.4 (s, H, Ar-NH); Z (CDCl₃): δ 1.3 (t, 3H, CH₃), 3.5 (bm, 2H, CH₂), 4.5 (d, 2H, CH₂), 9.7 (t, H, CH). The ¹H NMR spectra were recorded on a BRUKER 400 MHz spectrometer using D₂O/CDCl₃ as solvent and TMS as internal reference.

RESULTS

The oxidation of MTZ and TNZ with NBS was kinetically investigated at several initial concentrations of the reactants in HClO₄ medium. The salient features obtained for these two substrates are discussed separately.

Kinetics of Oxidation of MTZ

Under pseudo-first-order conditions ($[MTZ] \gg [NBS]$) and at constant $[HClO_4]$ and temperature, plots of $\log[NBS]$ vs. time were linear ($r > 0.990$) indicating a first-order dependence of rate on $[NBS]_0$. The calculated pseudo-first-order rate constants (k_{obs}) are given in Table 1. Further, the values of k_{obs} calculated from these plots were unaltered with variation of $[NBS]_0$, confirming the first-order dependence on

$[NBS]_0$. The rate was increased with increasing $[MTZ]_0$ (Table 1). Plot of $\log k_{obs}$ vs. $\log[MTZ]$ was linear (Fig. 1; $r = 0.985$) with a slope of unity, indicating a first-order dependence of the rate on $[MTZ]_0$. The rate of reaction was increased with increasing $[HClO_4]_0$ (in the range 0.001-0.005 M) (Table 1). The order with respect to $[HClO_4]$, as calculated from the slope of the plot of $\log k_{obs}$ vs. $\log [HClO_4]$ (Fig. 2), was found to be unity. Beyond 0.005 M HClO₄, retardation of the rate has been observed (Table 1), and the order with respect to $[HClO_4]$, as calculated from the slope of the plot of $\log k_{obs}$ vs. $\log[HClO_4]$ (Fig. 2) was found to be -1.03, indicating an inverse-first-order dependence of the rate on $[HClO_4]$. At constant $[H^+]$, addition of chloride ions in the form of NaCl increased the reaction rate, as shown in Table 2. From the plot of $\log k_{obs}$ vs. $\log[Cl^-]$ ($r = 0.998$), the order with respect to

Table 1. Effect of Varying Concentrations of Oxidant, Substrate and HClO₄ on the Reaction Rate at 308 K; $\mu = 0.1$ M; $[Hg(OAc)_2] = 0.001$ M

$10^4 [NBS]$ (M)	$10^3 [Sub]$ (M)	$10^3 [HClO_4]$ (M)		$10^4 k_{obs}$ (s ⁻¹)	
		MTZ	TNZ	MTZ	TNZ
1.0	8.0	3.0	7.0	2.58	3.69
3.0	8.0	3.0	7.0	2.61	3.71
5.0	8.0	3.0	7.0	2.64	3.49
7.0	8.0	3.0	7.0	2.74	3.55
9.0	8.0	3.0	7.0	2.81	3.61
5.0	4.0	3.0	7.0	1.40	1.83
5.0	6.0	3.0	7.0	2.38	2.52
5.0	10.0	3.0	7.0	3.57	5.36
5.0	12.0	3.0	7.0	4.81	5.90
5.0	8.0	1.0	4.0	0.90	2.01
5.0	8.0	2.0	5.0	1.79	2.41
5.0	8.0	4.0	6.0	3.38	3.02
5.0	8.0	5.0	8.0	3.92	3.99
5.0	8.0	6.0	9.0	3.11	4.66
5.0	8.0	7.0	-	3.01	-
5.0	8.0	8.0	-	2.29	-
5.0	8.0	9.0	-	2.02	-
5.0	8.0	10.0	-	1.78	-
^a 5.0	8.0	-	7.0	-	3.52
^b 5.0	8.0	-	7.0	-	3.46

^aAt ionic strength- $\mu = 0.15$ M. ^b $\mu = 0.2$ M.

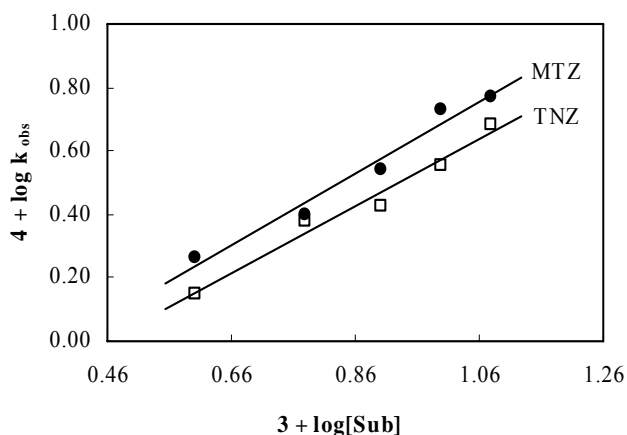


Fig. 1. Plot of $4 + \log k_{\text{obs}}$ vs. $3 + \log[\text{Sub}]$.

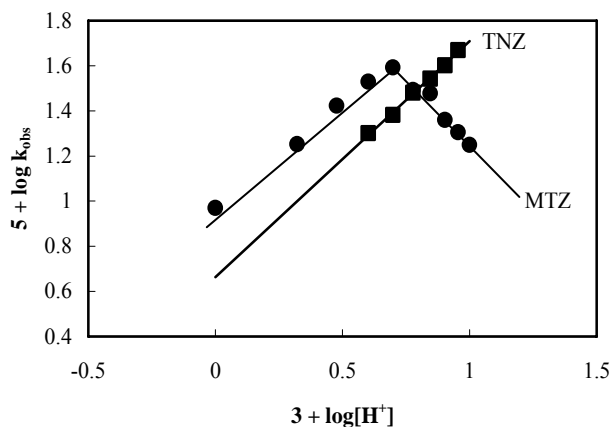


Fig. 2. Plot of $5 + \log k_{\text{obs}}$ vs. $3 + \log[\text{H}^+]$.

Table 2. Effect of Varying Concentration of Cl^- on the Reaction Rate at 308 K^a

$10^3 [\text{Cl}^-]$ (M)	$10^4 k_{\text{obs}}$ (s^{-1})	
	MTZ	TNZ
4.0	4.80	3.49
6.0	6.91	3.49
8.0	8.91	3.48
10.0	10.29	3.49
12.0	12.20	3.48

^aConditions: $[\text{NBS}] = 5 \times 10^{-4} \text{ M}$; $[\text{MTZ}] = [\text{TNZ}] = 8 \times 10^{-3} \text{ M}$; $[\text{H}^+] = 3 \times 10^{-3} \text{ M}$ (MTZ), $7 \times 10^{-3} \text{ M}$ (TNZ); $[\text{Hg}(\text{OAc})_2] = 1 \times 10^{-3} \text{ M}$; $\mu = 0.1 \text{ M}$.

Table 3. Effect of Varying Concentration of Succinimide on the Reaction Rate at 308 K^a

$10^4 [\text{RNH}]$ (M)	$10^4 k_{\text{obs}}$ (s^{-1})	
	MTZ	TNZ
2.0	2.18	3.45
4.0	1.70	3.49
6.0	1.50	3.47
8.0	1.32	3.48
10.0	1.10	3.42

^aConditions: $[\text{NBS}] = 5 \times 10^{-4} \text{ M}$; $[\text{MTZ}] = [\text{TNZ}] = 8 \times 10^{-3} \text{ M}$; $[\text{HClO}_4] = 3 \times 10^{-3} \text{ M}$ (MTZ), $7 \times 10^{-3} \text{ M}$ (TNZ); $[\text{Hg}(\text{OAc})_2] = 1 \times 10^{-3} \text{ M}$; $\mu = 0.1 \text{ M}$.

$[\text{Cl}^-]$ was found to be 0.72.

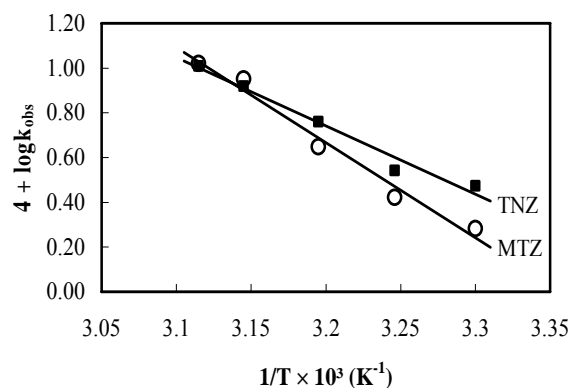
Addition of succinimide (RNH) to the reaction mixture retarded the reaction rate (Table 3). Further, a plot of $\log k_{\text{obs}}$ vs. $\log[\text{RNH}]$ was linear ($r = 0.999$) with a slope of -0.36 , indicating an inverse-fractional-order dependence of the rate on $[\text{RNH}]$. Variation of ionic strength of the medium (0.1-0.3 M) and addition of mercuric acetate (0.001-0.005 M) revealed no significant effect on the rate.

The effect of dielectric permittivity (D) of the medium on the reaction rate was studied by adding various proportions of CH_3CN (0-20% v/v) to the reacting system. It was observed that an increase in CH_3CN composition decreased the rate and a plot of $\log k_{\text{obs}}$ vs. $1/D$ gave a straight line ($r = 0.977$) with a negative slope. The values are reported in Table 4. The values of permittivity (D) for $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ mixtures are calculated from the equation, $D = D_w V_w + D_A V_A$, 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 showed that CH_3CN was not oxidized with NBS under the experimental conditions employed. The reaction was studied at different temperatures (303-321 K), keeping other experimental conditions constant. From the linear Arrhenius plot of $\log k_{\text{obs}}$ vs. $1/T$ (Fig. 3; $r = 0.999$) the values of activation parameters for the overall reaction were computed. The results are compiled in Table 5. The absence of free radicals during the course of oxidation was confirmed when no polymerization was initiated with addition of acrylonitrile

Table 4. Effect of Varying Dielectric Permittivity of the Medium on the Reaction Rate at 308 K^a

%CH ₃ CN (v/v)	D	10 ⁴ k _{obs} (s ⁻¹)	
		MTZ	TNZ
0	73.6	2.64	3.48
5	71.8	2.01	3.46
10	70.0	1.57	3.44
15	68.2	1.28	3.48
20	66.5	1.18	3.51

^aConditions: [NBS] = 5 × 10⁻⁴ M; [MTZ] = [TNZ] = 8 × 10⁻³ M; [HClO₄] = 3 × 10⁻³ M (MTZ), 7 × 10⁻³ M (TNZ); [Hg(OAc)₂] = 1 × 10⁻³ M; μ = 0.1 M.

**Fig. 3.** Plot of 4 + log k_{obs} vs. 10³/T.

solution to the reaction mixture.

Kinetics of Oxidation of TNZ

With substrate in excess at constant [HClO₄] and temperature, the [NBS]₀ was varied. Plots of log[NBS] vs. time were linear (r > 0.996) indicating a first-order dependence of the rate on [NBS]₀. The pseudo-first-order rate constants (k_{obs}) are listed in Table 1. The values of k_{obs} increased with increasing [TNZ]₀ (Table 1), and a plot of log k_{obs} vs. log [TNZ] was linear (Fig. 1; r = 0.987) with a slope of 1.03 indicating a first-order dependence of the rate on [TNZ]₀. Similarly, an increase in [HClO₄] increased the rate (Table 1) and from the linear plot of log k_{obs} vs. log[HClO₄]

Table 5. Effect of Varying Temperature on the Reaction Rate and Activation Parameters for the Oxidation of MTZ and TNZ^a

Temperature (K)	10 ⁴ k _{obs} (s ⁻¹)	
	MTZ	TNZ
303	1.92	2.97
308	2.64	3.49
313	4.45	5.76
318	8.94	8.29
321	10.47	-
323	-	10.2
E _a (kJ mol ⁻¹)	72.6	69.5
ΔH [‡] (kJ mol ⁻¹)	69.0	66.8
ΔG [‡] (kJ mol ⁻¹)	96.5	96.3
ΔS [‡] (J K mol ⁻¹)	-85.4	-94.1

^aConditions: [NBS] = 5 × 10⁻⁴ M; [MTZ] = [TNZ] = 8 × 10⁻³ M; [HClO₄] = 3 × 10⁻³ M (MTZ), 7 × 10⁻³ M (TNZ); [Hg(OAc)₂] = 1 × 10⁻³ M; μ = 0.1 M.

(Fig. 2; r = 0.998) an order obtained was unity, and hence showing the first-order dependence of the rate on [HClO₄].

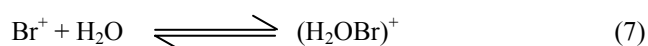
Variation of ionic strength of the medium (0.1-0.3 M), addition of succinimide (0.0002-0.001 M), halide ions and mercuric acetate (0.001-0.005 M) showed no significant effect on the reaction rate. The rate is unaffected by varying dielectric permittivity of the medium using CH₃CN (0-20% v/v). Kinetic activation parameters were calculated by studying the reaction at different temperatures (303-323 K). Plot of log k_{obs} vs. 1/T was shown in Fig. 3 and the results are given in Table 5. Absence of free radicals in the reaction mixture has been demonstrated by acrylonitrile test.

DISCUSSION

Reactive Species of NBS

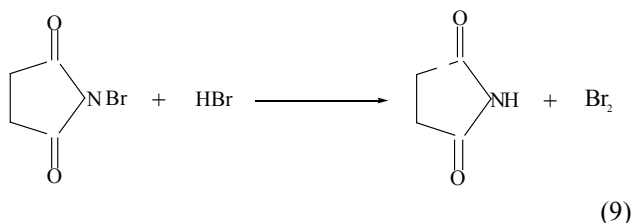
NBS is a two equivalent oxidant which oxidizes many substrates through NBS itself or Br⁺ or RN⁺HBr, or hypobromite anion. The reactive species responsible for the oxidizing character may depend on the pH of the medium [5]. Depending on the pH of the medium, NBS furnishes different types of reactive species in solutions [16-18] as shown in Eqs.

(3-8).



where R is $(\text{CH}_2\text{CO})_2$.

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

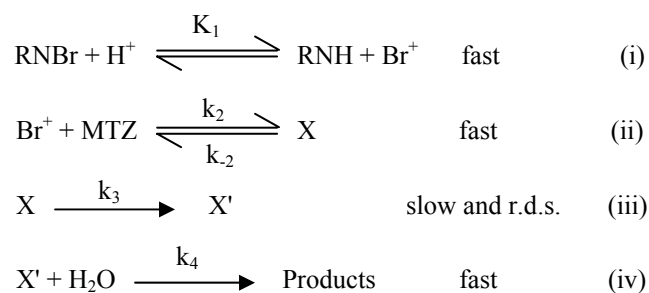


Mercuric(II) acetate acts as a capture agent for any Br^- formed in the reaction and exists as HgBr_4^{2-} or unionized HgBr_2 and ensures that oxidation takes place purely through NBS [19,20].

Mechanism and Rate Law for MTZ

Most investigations of NBS oxidations of organic substrates have assumed that, the molecular NBS acts only through its positive polar end [21,22]. However, since the nitrogen of the NBS will be protonated at the experimental concentrations of H^+ , in the present study, production of Br^+ is likely. At lower concentrations of H^+ (0.001-0.005 M) the positive effect of $[\text{H}^+]$ on the reaction rate observed allows us to assume either protonated NBS, *i.e.*, RN^+HBr or Br^+ or

$(\text{H}_2\text{OBr})^+$ as active oxidizing species. Further, negative effect of the initially added product, succinimide restricts us to take Br^+ as the oxidizing species. Bromonium ion has been proposed as a reactive species in many reactions [13,23]. On the basis of the above discussions and observed kinetic data, a probable mechanism (Scheme 1) is proposed for the oxidation of MTZ.



Scheme 1

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

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

Assuming steady state condition for X, it can be shown that,

$$[\text{X}] = \frac{K_1 k_2 [\text{RNBr}][\text{H}^+][\text{MTZ}]}{[\text{RNH}]\{k_{-2} + k_3\}} \quad (11)$$

On substituting Eq. (11) in Eq. (10), the following rate law [Eq. (12)] is obtained:

$$\text{rate} = \frac{K_1 k_2 k_3 [\text{RNBr}][\text{H}^+][\text{MTZ}]}{[\text{RNH}]\{k_{-2} + k_3\}} \quad (12)$$

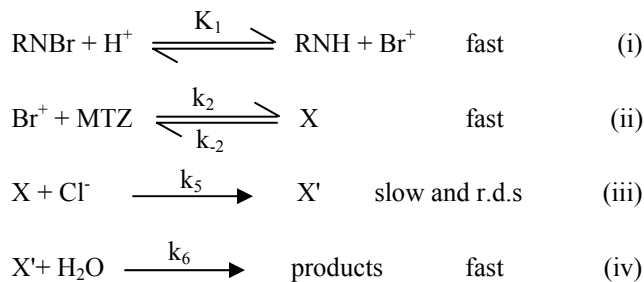
Since $\text{rate} = k_{\text{obs}}[\text{RNBr}]$, the rate law (12) can be transformed into Eq. (13),

$$k_{\text{obs}} = \frac{K_1 k_2 k_3 [\text{H}^+][\text{MTZ}]}{[\text{RNH}]\{k_{-2} + k_3\}} \quad (13)$$

Rate law (12) is in good agreement with the experimental results observed.

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

Mechanistic Investigation of Oxidation of Metronidazole and Tinidazole



Scheme 2

From slow step of Scheme 2

$$\text{rate} = \frac{-d[\text{RNBr}]}{dt} = k_5[\text{X}][\text{Cl}^-] \quad (14)$$

Applying steady state approximation for the species X and by solving for [X], one obtains,

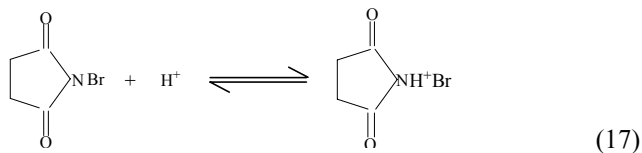
$$[\text{X}] = \frac{K_1 k_2 [\text{RNBr}][\text{H}^+][\text{MTZ}]}{[\text{RNH}]\{k_{-2} + k_5[\text{Cl}^-]\}} \quad (15)$$

By substituting [X] from Eq. (15) into Eq. (14), the following rate law [Eq. (16)] is obtained:

$$\text{rate} = \frac{K_1 k_2 k_5 [\text{RNBr}][\text{H}^+][\text{MTZ}][\text{Cl}^-]}{[\text{RNH}]\{k_{-2} + k_5[\text{Cl}^-]\}} \quad (16)$$

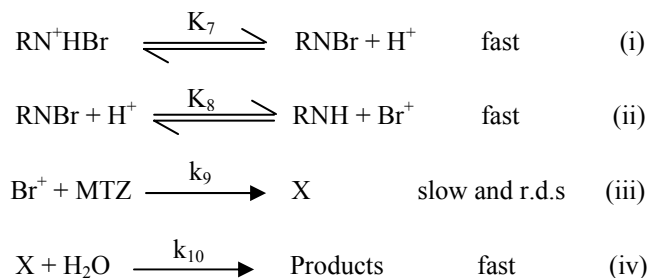
The rate law (16) clearly demonstrates the fractional-order dependence of the rate on [Cl⁻] and retardation of the rate by added succinimide and is also in good agreement with the experimental results.

At higher [H⁺] (0.006-0.01 M) the rate decreased with increasing [H⁺]. The inhibition nature of addition of H⁺ ions on the rate may be explained by assuming the following equilibria, and that the unprotonated species is the reactive one [24].



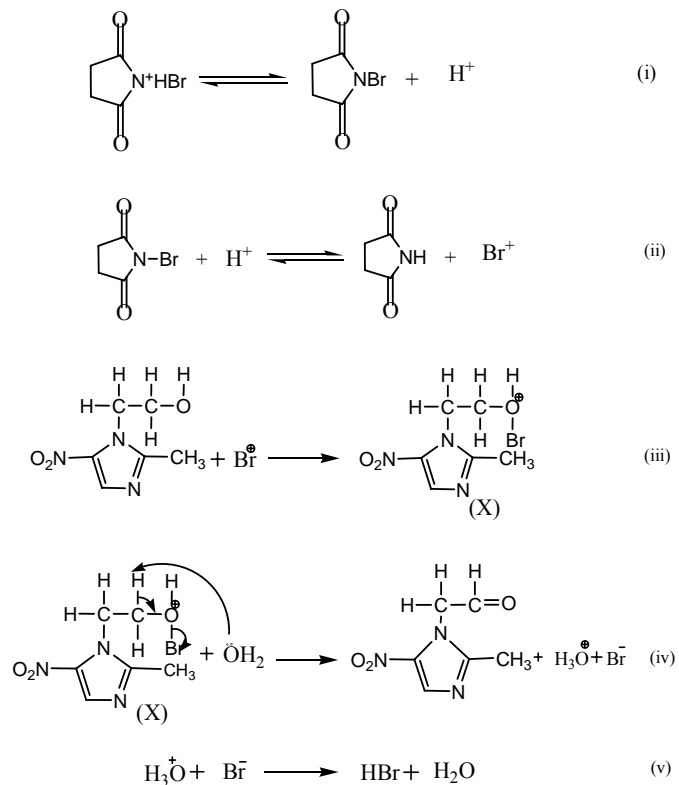
Under the present experimental conditions, the reaction is inverse-first-order with respect to [H⁺] and retardation of the rate by added succinimide. With the above results, a suitable

mechanism (Scheme 3) has been proposed for the oxidation of MTZ with NBS at higher H⁺ concentration.



Scheme 3

In Scheme 3, X is a Br⁺-MTZ complex whose structure is shown in Scheme 4, where a detailed mechanistic interpretation of MTZ oxidation with NBS in acid medium is proposed.



Scheme 4

Step (iii) of Scheme 3 determines the overall rate,

$$\text{rate} = \frac{-d[\text{RNBr}]}{dt} = k_9[\text{Br}^+][\text{MTZ}] \quad (18)$$

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

$$\text{RNBr}_t = [\text{RN}^+\text{HBr}] + [\text{RNBr}] + [\text{Br}^+] \quad (19)$$

From which, solving for $[\text{Br}^+]$ one obtains,

$$[\text{Br}^+] = \frac{K_7 K_8 [\text{RNBr}]_t [\text{H}^+]}{[\text{RNH}]\{K_7 + [\text{H}^+]\} + K_7 K_8 [\text{H}^+]} \quad (20)$$

By substituting Eq. (20) in Eq. (18), the following rate law [Eq. (21)] can be obtained:

$$\text{rate} = \frac{K_7 K_8 k_9 [\text{RNBr}]_t [\text{MTZ}] [\text{H}^+]}{[\text{RNH}]\{K_7 + [\text{H}^+]\} + K_7 K_8 [\text{H}^+]} \quad (21)$$

Since, $\text{rate} = k_{\text{obs}} [\text{RNBr}]_t$, Eq. (21) can be transformed into Eq. (22).

$$k_{\text{obs}} = \frac{K_7 K_8 k_9 [\text{MTZ}] [\text{H}^+]}{K_7 [\text{RNH}] + [\text{H}^+][\text{RNH}] + K_7 K_8 [\text{H}^+]} \quad (22)$$

The rate law (Eq. (21)) is in agreement with the experimental results.

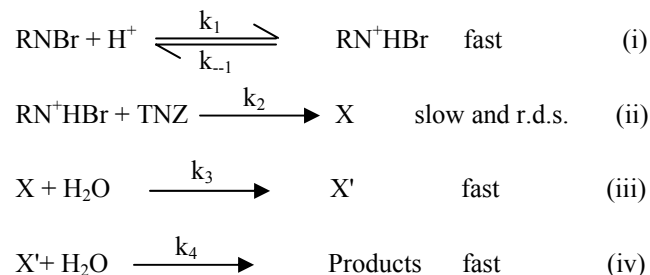
The proposed mechanism and the derived rate law are supported by the following experimental findings. A positive effect of dielectric permittivity of the medium provides support for the proposed mechanism. For the limiting case of zero angle of approach between two dipoles or an ion dipole system, Amis [25] showed that a plot of $\log k_{\text{obs}}$ vs. $1/D$ gives a straight line with a positive slope for a reaction between a positive ion-dipole interaction, whereas a negative slope for a reaction between a negative ion and a dipole or between two dipoles. The latter concept agrees with the present observations, where ion-dipole nature of the species involved in the rate determining step. The inhibition of added succinimide on the rate suggests its involvement in a fast equilibrium prior to the rate-determining step. The proposed mechanism is also supported by the fairly high values of energy of activation and other thermodynamic parameters. The high value of ΔH^\ddagger and the negative value of ΔS^\ddagger indicate that,

the transition state is more ordered than the reactants.

Mechanism and Rate Law for TNZ

The results of oxidation of TNZ with NBS in HClO_4 medium indicated the first-order dependence each on the concentration of NBS, TNZ and H^+ . Acceleration of the rate by increasing concentration of H^+ assumes that the protonated species of NBS, *i.e.*, $(\text{CH}_2\text{CO})_2\text{N}^+\text{HBr}$ is the most likely oxidizing species. It is known that NBS serves as a source of bromonium ion (Br^+) and undergoes a simple two-electron reduction leading to the formation of bromide ion, succinimide and the products of reaction [26]. The NBS as a source of bromonium ion gives product Br^- in presence of mercuric acetate. In the present investigation, the protonated NBS reacts with TNZ to form a complex which further undergo hydrolysis and intramolecular rearrangement to form products.

Considering the above facts and all experimental data, the following mechanism (Scheme 5) may be suggested for the oxidation of TNZ with NBS in acid medium:



Scheme 5

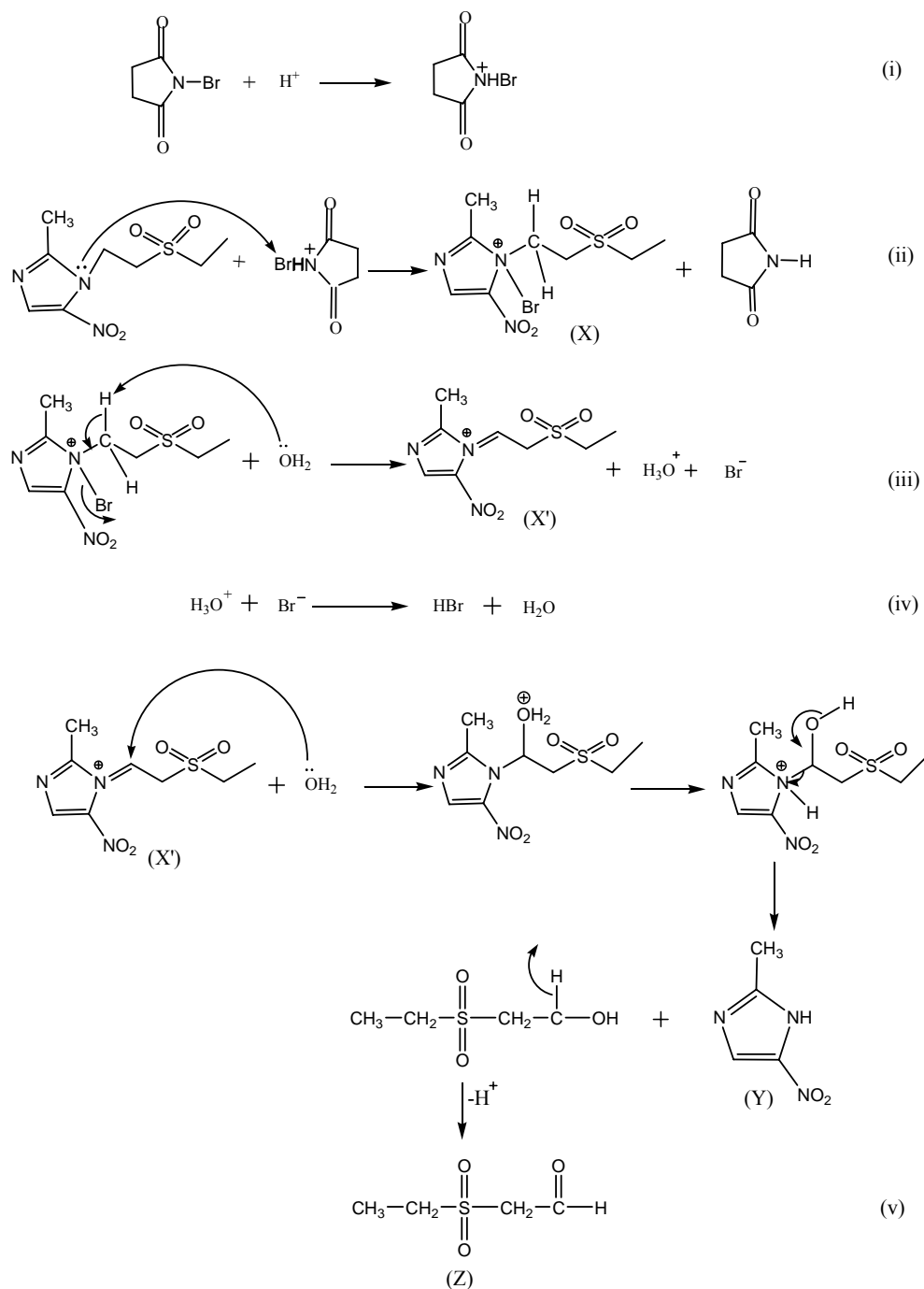
Here X and X' are the complex intermediate species whose structures are shown in Scheme 6, where a detailed mechanistic interpretation of NBS-TNZ reaction in acid medium is illustrated. From Scheme 5,

$$\text{rate} = k_2 [\text{RN}^+\text{HBr}] [\text{TNZ}] \quad (23)$$

Applying steady state conditions for RN^+HBr , it can be shown that,

$$[\text{RN}^+\text{HBr}] = \frac{k_1 [\text{RNBr}] [\text{H}^+]}{k_{-1} + k_2 [\text{TNZ}]} \quad (24)$$

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Scheme 6

Assuming that, $k_{-1} \gg k_2 [\text{TNZ}]$, then Eq. (24) can be written as,

$$[\text{RN}^+\text{HBr}] = \frac{k_1}{k_{-1}} [\text{RNBr}][\text{H}^+] \quad (25)$$

By substituting Eq. (25) in Eq. (23), the following rate law can be obtained:

$$\text{rate} = \frac{k_1 k_2}{k_{-1}} [\text{RNBr}][\text{H}^+][\text{TNZ}] \quad (26)$$

The rate law derived (Eq. (26)) is in agreement with the experimental results. The proposed Scheme 5 and rate law (26) are also substantiated by the experimental results discussed below.

It is noted that variation of the dielectric permittivity of the medium has no effect on the rate. An explanation can be offered by the Laidler equation [27], which relates the radius of the activated complex (r_{\ddagger}) with those of the reactants in the form [28,29],

$$\ln k' = \ln k_0 + \frac{3}{8kT} \left[\frac{2}{D} - 1 \right] \left[\frac{\mu_A^2}{r_A^3} + \frac{\mu_B^2}{r_B^3} + \frac{\mu^2}{r_{\ddagger}^3} \right] \quad (27)$$

Here k_0 is the rate constant in a medium of infinite dielectric permittivity and μ is the dipole moment. Under the conditions $r_{\ddagger}^3 = r_A^3 + r_B^3$, it would imply the absence of dielectric effect of solvent on the rate as observed in the present case.

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 (Table 5). The fairly high positive value of ΔH^\ddagger indicates that, the transition state is highly solvated while the high negative value of entropy of activation reflects the formation of a compact and a more ordered transition state.

CONCLUSIONS

It is concluded that the stoichiometry of the reaction in both MTZ and TNZ are the same. The oxidation product of MTZ is its corresponding aldehyde whereas TNZ undergoes oxidative cleavage with NBS to form 2-methyl-5-nitro 1H-imidazole and 2-ethyl sulfonyl acetaldehyde as products. Kinetic studies in acid medium reveal that, Br^+ and $(\text{CH}_2\text{CO})_2\text{N}^+\text{HBr}$ are the active oxidant species of MTZ and TNZ, respectively. In the case of MTZ, both acceleration and retardation of the rate have been noticed at lower (0.001-0.005 M) and higher (0.006-0.01 M) concentrations of HClO_4 , respectively. Based on the observed results plausible mechanisms are proposed and related rate laws have been deduced.

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