

# OXIDATION OF THE DRUG TRIMETAZIDINE BY N- BROMOSUCCINIMIDE IN AQUEOUS MEDIUM – A KINETIC STUDY

H.P. JAYADEVAPPA,\*<sup>a</sup>

<sup>a</sup>Department of Chemistry, Yuvaraja College, University of Mysore, Mysuru, India.

## ABSTRACT

*The kinetics of oxidation of Trimetazidine by N-bromo succinamide in perchloric acid medium has been studied at 303K. The products of oxidation were tested and stoichiometry of reaction was determined. The rate of reaction was observed to show a first order dependence on oxidant, fractional order on substrate and inverse fractional order on [H<sup>+</sup>]. The dielectric constant has a slight negative effect. The unchanged rate with ionic strength indicate involvement of non ionic species in rate determining step. The kinetic runs were performed at different temperature and thermodynamic parameters were computed. A mechanism consistent with observed parameters is proposed. Rate law is derived.*

**Keywords:** Trimetazidine, N-bromo succinamide, stoichiometry, oxidation, rate law.

## 1. INTRODUCTION

N-Halo amides have been successively used to perform a wide range of transformations as they react with variety of functional groups. With halogen in the +1 state, the N-haloimides are used for bromination and oxidation of organic compounds<sup>1-3</sup>. One such reagent N-bromo succinamide (NBS) is a potent oxidant and has been used in the quantitative determination of a variety of organic substrates. Its mild oxidising property due to source of positive halogen has been exploited for oxidation reactions in both acidic and alkaline medium<sup>5-7</sup>.

Trimetazidine (TMZ) is the first cytoprotective anti-ischemic agent and is a drug for angina pectoris<sup>6</sup>. It inhibits fatty acid metabolism and thereby improves myocardial glucose utilization. In diabetic patients with coronary heart disease it found to improve left ventricular function<sup>7</sup>. Recently, it has been shown to be effective in patients with heart failure of different etiologies<sup>8</sup>. Trimetazidine enhances glucose oxidation by inhibiting beta-oxidation of fatty acids by blocking long-chain 3-ketoacyl-CoA thiolase.

By the survey of literature it is revealed that, oxidation of TMZ by mild oxidants has not been reported. In the present study we are reporting kinetic and mechanistic aspects of TMZ oxidation by NBS in HClO<sub>4</sub> medium at 303 K.

## 2. MATERIAL AND METHODS

### 2.1 Experimental:

A solution of the NBS (E. Merck sample purified<sup>9</sup>) in distilled water was standardized by the iodometric method and preserved in brown bottle to prevent any further photochemical deterioration. Solution of the TMZ (Sigma-Aldrich) of required strength was freshly prepared each time. The other required reagents used were of analytical grade. Conductivity water was used for the kinetic studies. Concentrated solution of sodium per chlorate is used to maintain ionic strength. Methanol was added to maintain the dielectric constant. To keep pseudo first-order conditions excess of TMZ over NBS was maintained.

### 2.2 Kinetic measurements:

A mixture of solutions of TMZ, NaClO<sub>4</sub> and acid in required volumes was taken in a glass-stoppered Pyrex boiling tube. Requisite quantity of water was added to keep the total volume constant for all runs and thermostated at 303K. Required volume of equilibrated solution of NBS was added to the mixture and shaken

appropriately. The reaction progress was studied iodometrically by the estimation of unreacted NBS in a measured aliquot (5 mL) of the reaction mixture with time up to about two half-lives. The calculated pseudo first-order rate constants from the plots of  $\log [\text{NBS}]$  against time are reproducible within  $\pm 3\%$ .

### 2.3 Stoichiometry and product analysis :

The kinetic measurements performed at 303K by keeping excess of TMZ over NBS in  $\text{HClO}_4$  confirm the following stoichiometry that one mole of TMZ consumed two moles of NBS.



The reaction products were extracted with ether. The oxidation products of substrate substituted benzoic acid and piperazine from the ether layer are taken in to aqueous sodium hydroxide and hydrochloric acid solutions respectively and identified by TLC and GC-MS analysis. The reduction product of NBS, succinamide was extracted with ethyl acetate and confirmed by TLC.

## 3. RESULTS AND DISCUSSION

### 3.1 Effect of concentration of reactants on the rate:

Kinetic trails were carried out in pseudo-first order conditions ( $[\text{TMZ}] \gg [\text{NBS}]$ ) by varied  $[\text{NBS}]$ , at constant  $[\text{TMZ}]$ ,  $[\text{HClO}_4]$ , and temperature. The linear plots of  $\log [\text{NBS}]$  versus time are indicating a first-order dependence of reaction rate on  $[\text{NBS}]_0$ . From the slopes the pseudo first-order rate constants ( $k'$ ) were calculated (table 1). The  $k'$  values were unchanged on varying oxidant concentration further confirm the first-order dependence of the rate on  $[\text{NBS}]_0$ . Reactions were studied under similar experimental conditions by varying the concentration of  $[\text{TMZ}]$ . The  $k'$  values increased with increase in  $[\text{TMZ}]_0$  (table-1). The plot of  $\log k'$  versus  $\log [\text{TMZ}]_0$  is linear (figure-1) with a slope of 0.58 indicate fractional-order dependence on  $[\text{TMZ}]_0$ .

### 3.2 Effect of $[\text{H}^+]$ on the rate:

With increase in  $[\text{H}^+]$  using  $\text{HClO}_4$  decrease in rate was observed (table 1). Inverse fractional-order dependence of rate on  $[\text{H}^+]$  was indicated by linear plot of  $\log k'$  versus  $\log [\text{H}^+]$  (figure 1) with a negative slope of 0.43.

### 3.3 Effect of halide ions on the rate:

Added  $\text{Br}^-$  unchanged the rate ( $1 \times 10^{-3}$ - $10 \times 10^{-3}$  mol  $\text{dm}^{-3}$ ) indicate that they do not have significant effect on the rate of reaction.

### 3.4 Effect of ionic strength on the rate:

The varied ionic strength of the medium by the addition of  $\text{NaClO}_4$  ( $0.1 - 1.0$  mol  $\text{dm}^{-3}$ ) unchanged rate of reaction confirming the involvement of non ionic species in the rate limiting step.

### 3.5 Effect of dielectric constant on the rate:

Methanol was added (0 - 40 %, v/v) to vary dielectric constant of the medium, dielectric permittivity (D) of the medium decreased the rate of reaction as indicated by kinetic results (table-2). The plot of  $\log k'$  versus  $1/D$  is linear with a negative slope (figure-2). Methanol was ionized to very slight extent ( $< 1\%$ ) as confirmed by the blank experiments under the experimental conditions.

### 3.6 Effect of Succinamide concentration on the rate:

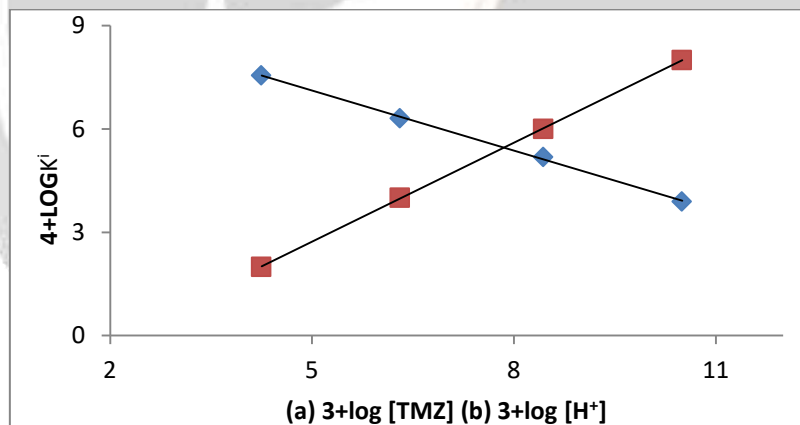
Succinamide ( $1 \times 10^{-3}$ - $10 \times 10^{-3}$  mol  $\text{dm}^{-3}$ ), the reduced product of oxidant NBS when added shows no significant effect on the rate indicating its non involvement in pre-equilibrium step.

### 3.7 Test for free radicals:

The reaction mixture when added to aqueous acrylamide fails to initiate polymerization indicating absence of any free radical species in the course of reaction.

**Table-1** Effect of oxidant, substrate and acid concentration on rate

$10^4$ [NBS] mol dm <sup>-3</sup>	$10^4$ [TMZ] mol dm <sup>-3</sup>	$10^4$ [HClO <sub>4</sub> ] mol dm <sup>-3</sup>	$K^1 10^4 S^{-1}$
2	4	4	6.23
4	4	4	6.31
6	4	4	6.35
8	4	4	6.26
4	2	4	4.25
4	4	4	6.31
4	6	4	8.44
4	8	4	10.50
4	4	2	7.55
4	4	4	6.31
4	4	6	5.18
4	4	6	3.89

**Fig -1** Effect substrate and acid concentration on rate**3.8 Effect of Succinamide concentration on the rate:**

**Succinamide** ( $1 \times 10^{-3}$ - $10 \times 10^{-3}$  mol dm<sup>-3</sup>), the reduced product of oxidant NBS when added shows no significant effect on the rate indicating its non involvement in pre-equilibrium step.

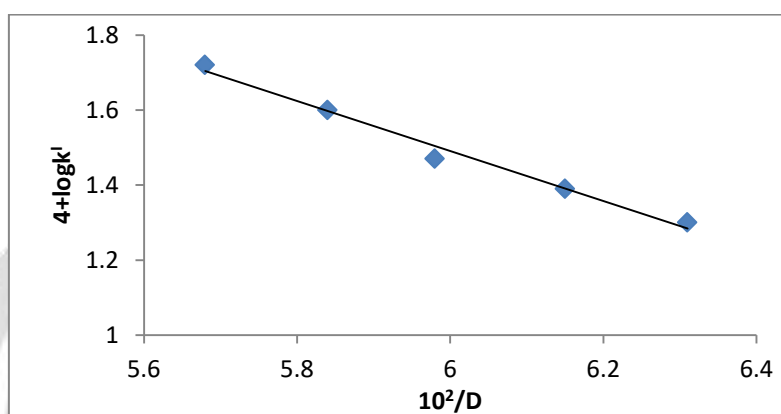
**3.9 Test for free radicals:**

The reaction mixture when added to aqueous acrylamide fails to initiate polymerization indicating absence of any free radical species in the course of reaction.

**Table-2 Effect of dielectric constant on rate**

MeOH % v/v	D	$10^2/D$	$K^1 10^4 S^{-1}$
0	76.7	1.30	6.31
10	72.4	1.39	6.15
20	67.4	1.47	5.98
30	62.7	1.60	5.84
40	58.1	1.72	5.68

$[NBS] = 4 \times 10^{-4} \text{ mol dm}^{-3}$ ,  $[TMZ] = 4 \times 10^{-3} \text{ mol dm}^{-3}$ ,  $[H^+] = 4 \times 10^{-3} \text{ mol dm}^{-3}$ ,  $\mu = 0.5 \text{ mol/dm}^{-3}$ .

**Fig -2 Effect of dielectric constant on rate**

### 3.10 Effect of temperature on the rate:

The kinetic runs were done at different temperature (303–323 K) keeping other experimental conditions constant (table-3). The activation parameters were computed from the linear Arrhenius plot of  $\log k^1$  versus  $1/T$  (figure-3).

**Table-3 Effect of temperature and activation parameters on rate**

Temperature (K)	$K^1 10^4(S^{-1})$	Thermodynamic parameter
298	5.02	$E_a = 15.15 \text{ kJ mol}^{-1}$
303	6.31	$\Delta H^\ddagger = 13.06 \text{ kJ mol}^{-1}$
308	7.65	$\Delta S^\ddagger = -212 \text{ J K}^{-1} \text{ mol}^{-1}$
313	9.02	$\Delta G^\ddagger = 75.62 \text{ kJ mol}^{-1}$
318	10.35	-

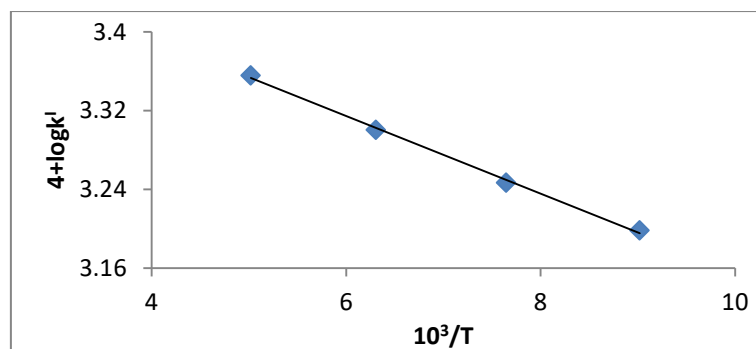
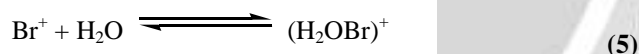
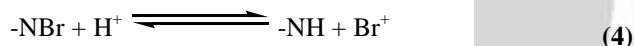


Fig -3 Effect of temperature on rate

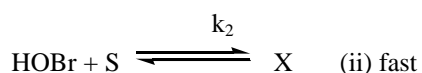
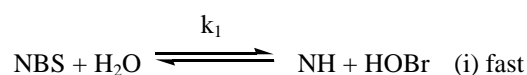
#### 4. DEDUCTION OF RATE LAW AND MECHANIAM

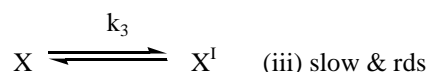
NBS behaves as a source of positive halogen in aqueous solution and this reagent has been exploited as an oxidant for a variety of substrates in both acid and alkali solutions. It gets reduced to succinamide thereby acts as mild oxidant with a two electron change<sup>14-21</sup>. It produces different ionic species with following equilibria in aqueous acidic solution.



In the present study the negative effect of  $[\text{H}^+]$  on the reaction rate observed allows us to assume the effect of  $[\text{H}^+]$  on the reaction rate. This allows us to assume either protonated NBS,  $\text{Br}^+$  or  $(\text{H}_2\text{OBr})^+$ , or HOBr as active oxidizing species and restricts us to take  $\text{Br}^+$  as the oxidizing species due to negative effect of the initially added product, succinimide. On the basis of observed kinetic data and above discussions, a probable mechanism (Scheme -1) is proposed for the oxidation. In scheme -2 the detailed plausible mechanism of reaction is picturized.

Let NBS represent the active oxidant, TMZ represent the substrate and X and  $\text{X}^1$  represent the intermediate complex species. The oxidation reaction is initiated by NBS through the attack of substrate to give an intermediate complex X. This complex eliminates a proton in the rate determining step to give the complex  $\text{X}^1$  which further reacts to give products.





Scheme 1.

For slow and rate determining step of scheme-1 the differential rate equation is

$$\frac{d[NBS]}{dt} = k_3 [X] \quad (6)$$

Let  $[NBS]_t$  be the effective total concentration of NBS, then

$$[NBS]_t = [HOBr] + [H_2OBr^+] + [X] \quad (7)$$

$$[NBS]_t = ([HOBr][H^+])/k_1 + \frac{[X]}{k_2[TMZ]} + [X] \quad (8)$$

On solving for X,

$$[X] = \frac{k_1 k_2 [NBS] [TMZ]}{[H^+] k_1 (1 + k_2 [TMZ])} \quad (9)$$

$$\frac{d[CAT]}{dt} = \frac{k_1 k_2 k_3 [NBS]_t [TMZ]}{[H^+] + k_1 (1 + k_2) [TMZ]} \quad (10)$$

The rate law derived agrees with the experimental results that a first, fractional and inverse fractional order dependence of reaction rate on  $[NBS]_0$ ,  $[AP]_0$  and  $[H^+]$  respectively.

Since rate =  $k^I [NBS]_0$ , from equation (9) we have,

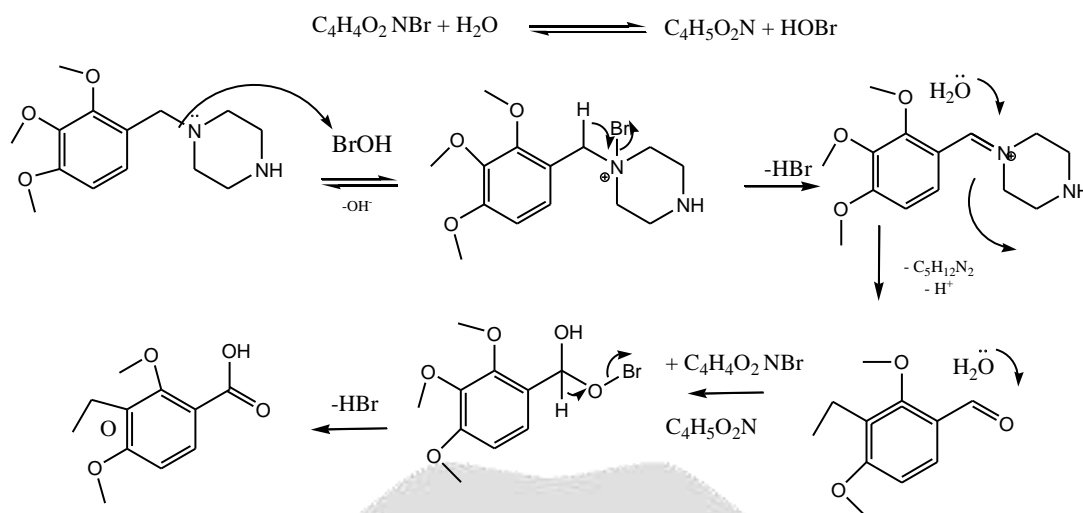
$$k^I = \frac{k_1 k_2 k_3 [TMZ]}{[H^+] + k_1 (1 + k_2) [TMZ]} \quad (11)$$

$$\frac{1}{k^I} = \frac{1}{k_2 k_3 [TMZ]} \left\{ \frac{[H^+]}{k_1} + 1 \right\} + \frac{1}{k_3} \quad (12)$$

From equations (11) and (12), plots of  $1/k^I$  versus  $1/[TMZ]$  and  $1/k^I$  versus  $[H^+]$  were linear (Figure 2). The values of  $k_1$ ,  $k_2$  and  $k_3$  were calculated from the slopes and intercepts.

Methanol in different proportions (0 - 40 %, v/v) is added to vary dielectric constant of the medium. The dielectric effect is negligible<sup>22-25</sup>. The reduction product succinamide when added fails to change the rate indicating its non involvement in pre-equilibrium. The rate remains same on varying ionic strength of the medium indicating the involvement of non-ionic species in the rate determining step. Bromide ions have no significant effect on the rate of reaction. Further the proposed mechanism is supported by the thermodynamic parameters computed from the experimental results. Formation of a properly ordered compact transition state complex with lesser degrees of freedom is supported by large negative value of entropy of activation and moderate positive values of free energy of activation and enthalpy of activation.





## 5. CONCLUSION

The redox reaction between NBS-TMZ has been carried out in aqueous medium. The reaction stoichiometry of 1:2 (eq.1) involving the TMZ oxidation by NBS has been observed. substituted benzoic acid and piperazine are the products of oxidation. The effect of dielectric constant and halide ions on reaction rate was studied. The thermodynamic parameters,  $E_a$ ,  $\Delta H^\ddagger$ ,  $\Delta G^\ddagger$ , and  $\Delta S^\ddagger$  have been computed From the Arrhenius plots. For the observed parameters a consistent mechanism has been proposed and rate law was derived

## 6. ACKNOWLEDGEMENT

The author gratitude to the Yuvaraja's College, University of Mysore, Mysore for providing laboratory facilities to perform the kinetic study.

## 7. REFERENCES

- Seliwanow, T., Ber. Deut. Chem. Ges., **26**, 423 (1983)
- Wohl, A. and Jaschinowski, K., Ber. Deut. Chem. Ges., **74**, 1243 (1941)
- Ziegler, K., Spath, A., Schaaf, E., Schumann, W. and Winkelmann, E., Justus Liebigs Ann. Chem., **551**, 80 (1942)
- Djerassi, C., Chem. Rev., **43**, 271 (1948)
- Arapahoe Chem. Inc. Technical Bulletin on "Positive Bromine Compounds", Boulder, Colorado, 1962.
- Fragasso G, Palloshi A, Puccetti P, Silipigni C, Rossodivita A, Pala M, Calori G, Alfieri O, Margonato A; J. Am. Coll. Cardiol. September 2006 **48** (5)
- Fragasso G, Rosano G, Baek Hong S, Sisakian H, Di Napoli P, Alberti L, Calori G, Kang SM, Sahakyan A, Vitale C, Marazzi G, Margonato A, Belardinelli R. Int J Cardiol. 2013; 163: 320-5
- Stanley WC, Marzilli M. Fundam Clin Pharmacol. April 2003. **17** (2): 133-45
- C. H. Depuy, M. Isaks, K. L. Eilers, and G. F. Morris. J. Org. Chem. 29, 3503 (1964)
- Ford. M.C. and Waters. W.A., J. Chem. Soc., 2240 (1952)
- Adam. J. Gosselain. P.A. and Goldfinger. P., Nature, **171**, 704 (1953)
- Skell. P.S. Tuleen D.L. and Readio. P.D., J. Am. Chem. Soc., **85**, 2850 (1963)
- Koenig. T. and Brewer. W., J. Am. Chem. Soc., **86**, 2728 (1964)
- Mcgrath. B.P. and Tedder. J.M., Proc. Chem. Soc. 80 (1961)
- F.D. Chattaway, J. Chem. Soc., Perkin Trans I, **1**, 145, **1905**
- B. Wiberg, physical chemistry, wiley, New York, **1964**
- J. Casado, M. Aturo Lopwz-Quintela and F.M. Lorenzobarral, J. Chem. Educ., 63, 450, 1986
- E. S. Amis. Solvent Effects On Reaction Rates and Mechanism, Academic Press, New York., **1966**, 1672.
- Laidler. Chemical Kinetics, Tata Mc Graw-Hill, New Delhi, **1995**, 211.
- G. M. G. Ramananda, S. Ananda. Kinetics and mechanism of oxidation of o-toluidine by sodium -N-chloro benzene sulphonamide in acid medium. *Asian. J. Chem*, **1999**, 11(4), 1348-1352.
- G. Akerlof. *J. Am. Chem. Soc*, **1932**, 54, 4125.