ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Kinetic and Mechanistic Studies on the Oxidation of Tinidazole By Bromamine-T (Bat) in Hcl Medium

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ABSTRACT

The kinetics of the oxidation of Tinidazole (TNZ)-1-(2-ethylsulfonylethyl)-2-methyl-5-nitro-imidazole by sodium salt of bromamine-T-(BAT;N- bromo-p-toluene sulfonamide-p-CH_3 $C_6H_4SO_2NBrNa.3H_2O$) in HCl medium has been studied at 303 K. The oxidation reaction follows first order with respect to $[BAT]_0$ $[TNZ]_0$ and $[HCl]_0$. Addition of, p-toluene sulfonamide (PTS), a reduction product of BAT and the ionic strength ($NaClO_4$) of reaction medium shows negligible effect on the oxidation rate. The reaction mixture fails to induce polymerization of acrylonitrile suggesting the absence of in situ free-radical formation. The presence of halide ions and (H^+) ions exhibit significant effect on the reaction rate. The dielectric constant is negative. The Michaelis-Menten type of kinetics has been proposed and activation parameters (Ea, $\Delta H^{\#}$, $\Delta S^{\#}$, $\Delta G^{\#}$) for the rate determining step and the composite reaction have been determined. Formation and decomposition constant have been evaluated. The protonated oxidant $C_6H_5CH_3SO_2NH_2Br^+$ is the active oxidizing species and it react with TNZ. The oxidation product of TNZ has been characterized. A probable mechanism consistent with the kinetic data has been proposed.

Key wards: Oxidation Kinetics, Tinidazole, Bromamine-T, Acid medium

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ISSN: 0975-8585

INTRODUCTION

Aromatic-N-haloamides are mild oxidants containing a strong polarized N-linked halogen which is in +1 state. BAT, a better oxidizing agent, can be easily prepared from the bromination of chloramine-T (CAT). The BAT is a recent addition to the class of haloamines and was employed as an oxidometric titrant in aqueous medium[1]. A review of literature shows that kinetic studies with BAT reagent are meagerin comparison with CAT [2]. Tinidazole [1-(2-ethylsulfonylethyl)-2-methyl-5-nitroimidazole (TNZ)] belonging to nitro imidazole group of drug used to treat infections such as ameobiasis, giardiasis and trichomoniasis. The kinetics of oxidation of TNZ with bromamine-T (BAT) in hydrochloric acid medium has been investigated at 303 K. Literature survey revealed no information on the oxidation of this drug with any oxidant from its kinetic and mechanistic aspects. The Kinetics and mechanistic oxidation of Tinidazole (TNZ) by BAT in HCl medium have been studied at 303 K.

MATERIALS AND METHODS

EXPERIMENTAL

Bromamine- T was obtained by partial-debromination of dibromamine-T (DBT) in 4M NaOH[3]. The compound can be prepared by dissolving Chloramine- T (10g) in 200 ml water to it a liquid bromine (2 ml) is added with constant stirring. The precipitate of BDT (golden yellow) so obtained is thoroughly washed with water, filtered under suction and dried in vacuum desiccators for 24 hours. The purity of the sample is checked by the elemental analysis for N, S and Br (found: N=4.3%, S=9.6%, Br=48.5%; Required N=4.26%, S=9.73%, Br=48.56%). The dry sample melts at 92-93° C with decomposition. About 33g of the prepared DBT were dissolved in small lots at time and with stirring, in 50ml of aqueous 4M NaOH and the solution was cooled in ice. Pale yellow crystals of BAT separated out. They were filtered under suction, washed quickly with the minimum quantity of water and dried over. The yield was 28g (found: Br= 24.4%, N=4.4%, S=9.8%, required for BAT, Br= 24.5%, N= 4.3% S= 9.8%). On heating in the air, the compound gave a white residue of sodium bromide, the loss of weight on heating being the theoretical weight loss of 68.4% for the conversion.

$$Na^{+}(CH_3C_6H_4SO_2NBr)^{-}\,3\,H_2O \longrightarrow Na^{+}\,Br^{-}$$

The purity of BAT obtained was checked iodometrically and through its mass, UV, IR and ^{1}H and ^{13}C NMR data. An aqueous solution of BAT was prepared, standardized by the iodometric method, and preserved in brown bottles.

Tinidazole obtained from Embiotic Laboratories (P) Ltd. was used without further purification. All solutions ware prepared using AR chemicals and double distilled water. The ionic strength of the medium was adjusted to required value using a concentrated solution of sodium perchlorate.

ISSN: 0975-8585

Kinetic Measurement

The reaction was carried out in a glass -Stoppard Pyrex boiling tubes whose outer surface was coated black to eliminate photochemical effects. Requisite amount of the solutions of TNZ, HCl and Water (to keep the total volume constant for all runs) were taken in the boiling tube and thermostated at 303 K for thermal equilibrium. A measured amount of the oxidant solution which is also thermostated at the same temperature, has rapidly added to the mixture with stirring in the boiling tube. The progress of the reaction was monitored by iodometric determination of the unreacted oxidant in measured aliquots (5 ml each) of the reaction mixture withdrawn at different intervals of time. The course of the reaction was studied for two half-lives. The calculated pseudo-first-order rate constants ($k^{/}$) were reproducible within ($\pm$ 3%).

Stoichiometry

Various ratios of Tinidazole and BAT were equilibrated in presence of 3 x 10^{-3} mol dm^{-3} HCl at 303 K under the conditions [BAT] >> [TNZ]. Determination of the unreacted oxidant in the reaction mixture showed that one mole of tinidazole consumed one mole of oxidant confirming the following stoichiometry.

$$C_8H_{13}O_4N_3S + TsNBrNa + H_2O \rightarrow C_4H_5O_2N_3 + C_4H_8O_3S + TsNH_2 + H^+ + Br^-$$

The reduction product of the oxidant, p-Toluene sulfonamide was detected by thinlayer chromatography using light petroleum-chloroform-1-butanol (2: 2: 1) as the solvent and iodine as the reducing agent[4]. Further confirmed by IR spectral data and MS. Further it was confirmed by its MP 138 - 143°C (M P: 136° C– 140°C).

The oxidation product 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 **[5]**, and identified as 2-methyl-5-nitro-1H-imidazole **(A)** and 2-ethyl sulphonyl acetaldehyde **(B)** by its ^{1}H NMR spectral studies[6]. **A** (D_2O): δ 2.4(s, 3H, CH_3), 7.9 (s, H, Ar-H), 13.4 (s, H, Ar-NH); **B** ($CDCl_3$): δ 1.3 (t, 3H, CH_3), 3.5 (bm, 2H, CH_2), 4.5 (d, 2H, CH_2), 9.7 (t, H, CH). The ^{1}H NMR spectra were recorded on a BRUKER 400 MHz spectrometer using $D_2O/CDCl_3$ as solvent and TMS as internal reference. 2-ethyl sulphonyl acetaldehyde also detected by 2, 4 DNP test.

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RESULTS

Effect of the Reactants

a) Effect of BAT

The kinetics of oxidation of TNZ by BAT was investigated at several initial concentrations of reactants in acid medium. The experiments conducted under pseudo-order conditions i.e., [TNZ] >> [BAT] at constant [TNZ], [HCl] and temperature, plots of log $[BAT]_0$ vs. time, were made and found to be linear, (plots are not shown). The rate constant did not change in $[BAT]_0$ confirming the first order dependance on the reaction rate of $[BAT]_0$. [Table 1].

Table 1 Effect of reactants, medium, halide ion concentrations on the reaction rate

10^4 [BAT]/M	10^4 [TNZ]/M	10^4 [HCl]/M	10^2 [NaCl]/M	10^2 [NaBr]/M	10^4 k/S
5.0	10	3	_	_	3.5
10	10	3	_	_	3.6
20	10	3	_	_	3.5
30	10	3	_	_	3.7
10	5.0	3	_	_	0.98
10	10	3	_	_	3.63
10	20	3	_	_	8.53
10	30	3	_	_	18.60
10	10	30	_	_	3.63
10	10	40	_	_	4.16
10	10	50	_	_	5.87
10	10	80	_	_	7.00
10	10	100	_	_	10.80
10	10	3	1	_	5.5
10	10	3	5	_	8.2
10	10	3	10	_	16.1
10	10	3	_	1	1.3
10	10	3	_	5	0.9
10	10	3	_	10	1.0

I=5 x 10^{-3}mol dm^{-3} T= 303 K

b) Effect of TNZ

Under identical experimental conditions, an increase in the [TNZ] leads to an increase in the k' values (Table 1) at constant $[BAT]_0$ $[HCl]_0$ and temperature showing a first order (1.0) dependence of the rate on [TNZ]. Plots of log k' vs. log [TNZ] were linear (fig.1) with unit slopes showing first order dependence of the rate on the [TNZ]. [Table 1]

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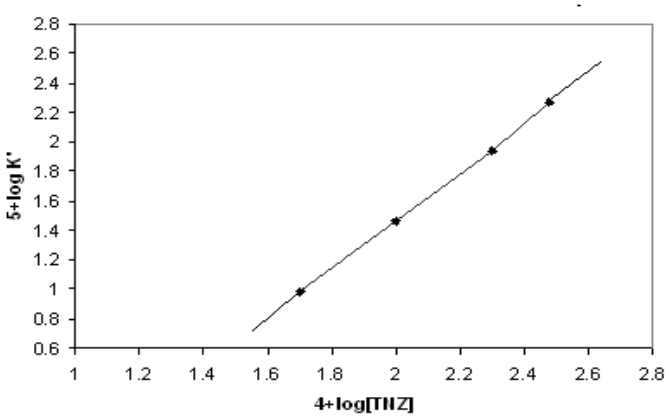

Fig.1. Effect of Tinidazole in HCl medium [oxidation of Tindazole>< Broamine – T]

Effect of HCl

When [HCl] was increased, keeping at constant [TNZ], [BAT] and temperature, resulted in an increased rate. Plots of log $k^{/}$ vs [HCl] were linear **(**fig 2) with positive slope of (0.9) indicating a first order dependence in [HCl]. [Table1]

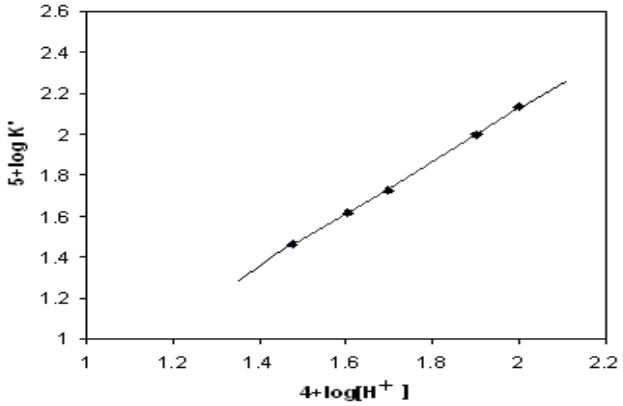

Fig.2. Effect of HCl medium [oxidation of Tindazole>< Broamine – T]

Effect of Halide ions

At constant $[H^+]$ =3 x 10^{-3} mol dm^{-3} of HCl, addition of NaCl (1 x 10^{-2} mol dm^{-3} to 10 x 10^{-2} mol dm^{-3}), keeping at constant $[TNZ]_0$ $[BAT]_0$ and temperature, resulted in an increased rate. Plots of log $k^{/}$ vs [NaCl] were linear (fig 3) with positive fractional slopes (0.81) indicating a first order in [NaCl]. [Table 1]

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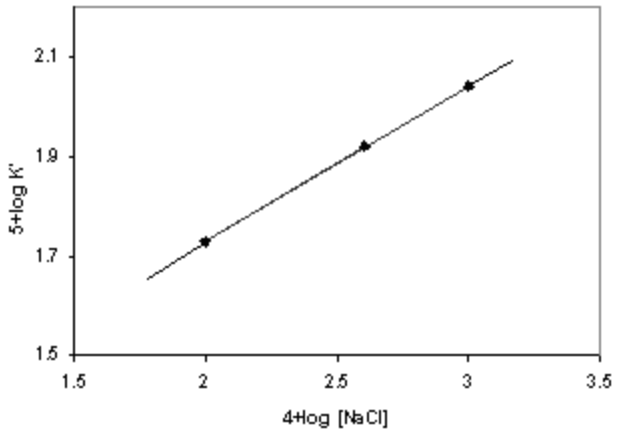

Fig.3. Effect of NaCl [oxidation of Tindazole>< Broamine – T]

Effect of p-Toluene sulfonamide (PTS)

Under suitable experimental conditions, the addition of the reduction product of oxidant, p-Toluene sulfonamide (0.5 x 10^{-3} mol dm^{-3} to 2 x 10^{-3} mol dm^{-3}) in the reaction, it was not effected on the rate of the reaction [Table 2], which indicates its non-involvement in a pre-

Table 2 Effect of $NaClO_4$ and PTS concentration on the reaction rate.

10^2 [$NaClO_4$.] Mol dm^{-3}	$10^4 k^{/} s^{-1}$	10^3 [PTS] Mil dm^{-3}	$10^4 k^{/} s^{-1}$
1	2.26	0.5	2.64
2	2.37	1	2.49
50	1.96	2	2.44

[BAT]= 1x10^{-3}mol dm^{-3} ; [TNZ] = 10x10^{-3}mol dm^{-3} ; I=5x10^{-3}mol dm^{-3}; [HCl]=3x10^{-3}mol dm^{-3} ; T=303K

Effect of Ionic strength (I)

The variation of ionic strength using the solution of $NaClO_4$ (1 x 10^{-3} mol dm^{-3} to 5 x 10^{-3} mol dm^{-3}) did not effect on the rate of the reaction [Table 2], indicating that non-ionic species are involved in the rate limiting step.

c) Effect of Dielectric constant of Medium

The dielectric constant (D) of the medium was varied by adding methanol to the reaction mixture. An increase in the addition of the methanol resulted in a decrease of the rate of the reaction. Plots of dielectric constant [D] vs. log $k^{/}$ were made (Table 3) and slopes were found to be linear [fig 4] with the negative order.

Table 3 Effect of dielectric constant of medium on the reaction rate.

[MeOH]	D	10^2/D	$10^4 k s^{-1}$

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% v/v			
0	76.73	1.3032	3.63
10	72.37	1.3817	1.66
20	67.48	1,4819	0.833
30	62.71	1.5946	.385

[BAT]= $1x10^{-3}$mol dm^{-3} ; [TNZ] = $10x10^{-3}$mol dm^{-3}; I=$5x10^{-3}$mol dm^{-3}; [HCl]= $3x10^{-3}$ mol dm^{-3} ; T=303K

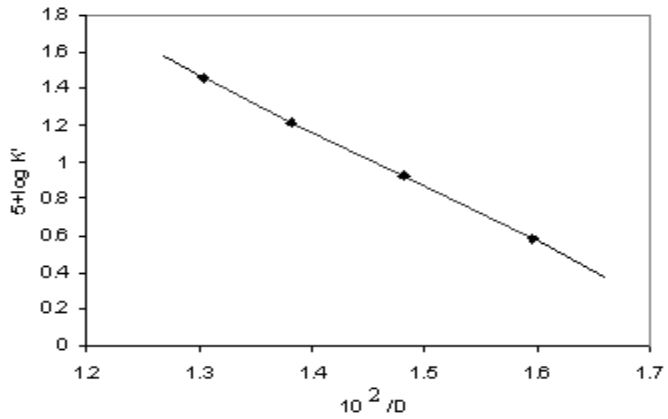

Fig.4. Effect of Methanol [oxidation of Tindazole>< Broamine – T]

d) Effect of temperature

The reaction was studied over a range of the temperature 303 K to 313 K, by varying the concentration of Tinidazole and keeping the other experimental conditions constant**.** [Table 4]. It was found that the rate of the reaction increased with the increase in the temperature (fig 5). From the linear Arrhenius plot in (fig 5), log $k^{/}$ vs.1/T gave energy of activation (E_a) from which other activation parameters like the enthalpy of activation ($\Delta H^{\#}$), entropy of activation ($\Delta S^{\#}$) and free energy of activation ($\Delta G^{\#}$) were computed. The Data is given in the [Table 5]. The experiment is conducted by varying the concentration of TNZ at different temperature (293 K-313 K) (fig 6).

Table 4 Effect of TNZ concentration on the reaction rate at different temperatures.

10^3[TNZ] mol dm^{-3}	$10^4 k\ s^{-1}$		
	293K	303K	313K
5	0.19	0.959	1.33
10	1.2	3.63	4.58
20	3.1	8.53	13.57

[BAT]= $1x10^{-3}$mol dm^{-3} ; I=$5x10^{-3}$mol dm^{-3} ;[HCl]= 3 x 10^{-3} mol dm^{-3}

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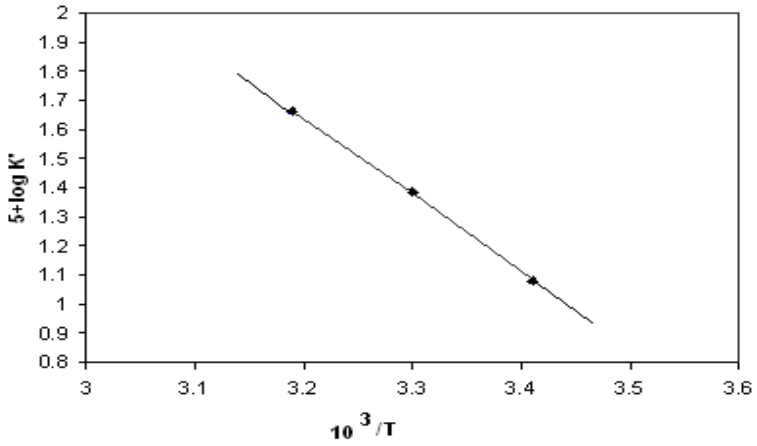

Fig.5. Effect of Temperature (standard condition) [oxidation of Tindazole>< Broamine – T]

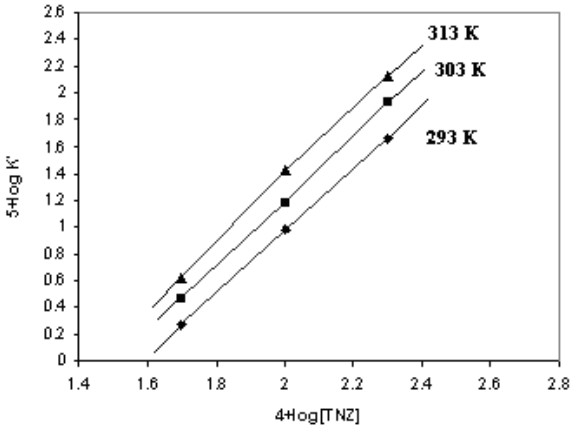

Fig.6. Effect of substrate at different temperature in acid medium[oxidation of Tindazole>< Broamine– T]

Test for free radicals

The addition of the reaction mixture to the aqueous acrylamide solution did not initiate polymerization, showing the absence of the free radical species during the reaction sequences.

DISCUSSION

N-halo amines are mild oxidants generally undergo a two electron change per mole in its reactions [7]. Depending the p^H of the medium these halo amines generate different types of species in solution**.** Bishop and Jennings [8], Pryde and Soper[9], Morris et al[10] and Hardy and John ston[11] have shown the existence of similar equilibrium in acid and alkaline solutions of N-halo amines. Bromamine-T and Bromamine-B like Chloramine –T and Chloramine –B behave as strong electrolytes in aqueous solutions forming different species of the following types:

$$TsNBrNa \rightleftharpoons TsNBr^- + Na^+ \quad (1.1)$$

$$TsNBr^- + H^+ \rightleftharpoons TsNHBr \quad (1.2)$$

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$$2\,TsNHBr \rightleftharpoons TsNH_2 + TsNBr_2 \quad (1.3)$$

$$TsNHBr + H_2O \rightleftharpoons TsNH_2 + HOBr \quad (1.4)$$

$$TsNBr_2 + H_2O \rightleftharpoons TsNHBr + HOBr \quad (1.5)$$

$$TsNHBr + H^+ \rightleftharpoons TsNH_2Br^+ \quad (1.6)$$

$$TsNH_2Br^+ + H2O \rightleftharpoons TsNH_2 + H_2O^+Br \quad (1.7)$$

$$HOBr \rightleftharpoons H^+ + OBr^- \quad (1.8)$$

$$HOBr + H^+ \rightleftharpoons H_2O^+Br \quad (1.9)$$

(Here Ts = p-CH_3 $C_6H_4SO_2$ for BAT)

Therefore, the possible oxidizing species in acid medium are RNHBr, $RNBr_2$, HOBr and probably H_2O^+Br and in alkaline solution RNHBr, HOBr, $RNBr^-$ and OBr^-. In the present case of BAT, if RSO_2NBr_2 were to be reactive species, the rate law predicts a second order dependence of rate on [BAT] and a negative effect of p-CH_3 $C_6H_4SO_2NH_2$ is expected according to the equation [1.3], but both are contrary to the experimental observations. If HOBr is primarily involved, a first order retardation of rate by the added PTS is expected.

Hardy and John ston[11], who have studied the p^H dependent relative concentrations of the species present in acidified halo amine solutions of comparable molarities, have "Shown that CH_3 Ph SO_2 NHBr is likely oxidizing species in acid medium". Narayanan and Rao[12] and Subhashini et al[13] have reported that mono haloamines can be further protonated at p^H 2, as shown in equations [2.0] for Chloramine-T.

$$p\text{-}CH_3\,C_6H_4SO_2NHCl + H^+ \rightleftharpoons (p\text{-}CH_3\,C_6H_4SO_2NH_2Cl)^+ \quad [2.0]$$

The results of oxidation of TNZ with Bromamine-T in HCl medium indicated the first order dependence each on the concentration of BAT, TNZ and H^+. The increase in the rate by increasing concentration of H^+ assumes that the protonated species of BAT and the reaction indicates that the rate increases with increase in Cl^- ion in the presence of sodium chloride salt. Therefore in the present investigation it was proposed that
Ts NH_2Br----Cl is the reactive species.

$$Ts\ NHBr + H^+ + Cl^- \overset{K_1}{\rightleftharpoons} Ts\ NH_2Br\text{---}Cl \quad (X) \qquad \text{(i) fast}$$

$$Ts\ NH_2Br\text{----}Cl + TNZ \xrightarrow{k_2} (X^/) \qquad \text{(ii) slow and r.d.s.}$$

$$X^/ \xrightarrow{k_3} Product \qquad \text{(iii) fast}$$

Scheme-1

Here X and $X^/$ are complex intermediate species whose structures are shown in Scheme-2. Where a detailed mechanistic interpretation of BAT-TNZ in acid medium is illustrated.

From scheme-1

$$K_1 = \frac{[TsNHBr][H^+][Cl^-]}{[TsNH_2Br---Cl]} \quad (1)$$

$$[TsNH_2Br---Cl] = \frac{[TsNHBr][H^+][Cl^-]}{K_1} \quad (2)$$

$$\therefore \text{ Rate } = k_2[TsNH_2Br---Cl][TNZ] \quad (3)$$

By substituting equation (2)

$$\therefore \text{Rate} = \frac{k_2[TsNHBr][H^+][Cl^-][TNZ]}{K_1} \quad (4)$$

The rate law derived (eqn. 4) is in agreement with the experimental results. The proposed scheme 1 and rate law (eqn 4) are also substantiated by the experimental results. It is noted that variation of dielectric permittivity of the medium has no effect on the rate.

The negligible influence of added p-toluene sulphonamide showing that it is not involved in pre-equilibrium.

The rate on dielectric constant was found to be negative, with the rate decreasing in solvent mixtures of lower polarity than water. Hence it supports the interaction of two dipole in the rate limiting step of the proposed mechanism.

CONCLUSION

Variation of ionic strength of the medium does not alter the rate indicating that non-ionic species are involved. The mechanism is also supported by the moderate values of energy of activation. The fairly high positive values of free energy of activation and enthalpy of activation indicate that the transition state is highly solvated, while the negative entropy of activation reflects the formation of the compact and more ordered transition state. All these are consistent with the proposed mechanism.

ACKNOWLEDGEMENT

The authors thank Kuvempu University Karnataka, India for providing the lab facilities to bring about this work. First author thanks to Management of Dayananda Sagar Institutions, Bangalore, for permission to carry out research at the Department of Post-Graduate Studies in Chemistry, Kuvempu University, Shimoga. Embiotic Laboratories (P) Ltd. Kumbalgodu, Bangalore and Additional drug controller (H.Q), Bangalore for providing the drug samples to carry out the research work.

ISSN: 0975-8585

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