

## Research Article

# Kinetics and Mechanistic Studies on Oxidation of Levocarnitine by Bromamine-T in HCl Medium Catalyzed by Ru(III)

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A kinetic study on RuCl<sub>3</sub>-catalysed oxidation of levocarnitine (LC) by sodium N-bromo-*p*-toluenesulphonamide or bromamine-T (BAT) has been carried out in HCl medium at 303 K. The reaction rate shows a first order dependence on [BAT]<sub>0</sub> and fractional order with respect to both [LC]<sub>0</sub> and [H<sup>+</sup>]. Addition of the reaction product, *p*-toluenesulphonamide, retards the rate. The addition of RuCl<sub>3</sub> and chloride ions to the reaction mixture shows an increase in the rate of the reaction. The dielectric effect is positive. The variation of ionic strength of the medium has no significant effect on the rate of the reaction. The reaction fails to initiate polymerization of acrylamide. Michaelis-Menten type of kinetics has been proposed. Thermodynamic parameters have been computed from Arrhenius plot by studying the reaction at different temperatures. The reaction stoichiometry and oxidation products were identified. Based on the experimental observations a suitable mechanism was proposed and rate law deduced.

## 1. Introduction

Levocarnitine ((R)-(-3-carboxy-2-hydroxypropyl)trimethylammonium chloride) is a carrier molecule in the transport of long chain fatty acid across the inner mitochondrial membrane. It is a naturally occurring substance required in mammalian energy metabolism. It has been shown to facilitate long chain fatty acid entry into cellular mitochondria, thereby delivering substrate for oxidation and subsequent energy production.

Levocarnitine may also alleviate the metabolic abnormalities of patients with inborn errors that result in accumulation of toxic organic acids [1, 2].

N-haloamines are mild oxidants and generally undergo a two electron change per mole in its reactions. They act as sources of halonium cations, hypohalite species, and N-anions, which act both as bases and nucleophiles [3]. There are many reports on N-halocompounds behaving as oxidizing agents [4–7]. However, a review of literature shows that kinetic studies with Bromamine-T (BAT) are meagre [8, 9].

Literature survey shows that there is no information available on the kinetics and oxidation of levocarnitine by any oxidizing agents from the mechanistic view point. There

was a need for understanding the mechanism of oxidation of this drug, so that this study may throw some light on the metabolic conversions in the biological system. The reaction of LC with BAT in HCl medium was found to be sluggish but the reaction was found to be facile in the presence of RuCl<sub>3</sub> catalyst. Therefore, in the present communication, we report the kinetics and mechanism of oxidation of levocarnitine by bromamine-T in HCl medium catalyzed by RuCl<sub>3</sub> at 303 K.

## 2. Experimental

Bromamine-T was prepared [10] by partial debromination of dibromamine-T (DBT). Its purity was checked by iodometry for its active bromine content. An aqueous solution of BAT was standardized iodometrically and stored in brown bottles to prevent any of its photochemical deterioration. Levocarnitine (Biocon Ltd.) was used as received. The aqueous solution of the substrate was prepared freshly each time. All the other chemicals used were of analytical grade of purity. Doubly distilled water was used for all the measurements. A constant ionic strength of the medium was maintained ( $\mu = 0.5 \text{ mol dm}^{-3}$ ) using concentrated solution of NaClO<sub>4</sub>.

**2.1. Kinetic Procedure.** The reactions were carried out under pseudo-first order conditions by keeping an excess of levocarnitine over BAT in glass-stoppered pyrex boiling tubes coated black on outside to eliminate photochemical effects. Oxidant and the requisite amounts of substrate, HCl, RuCl<sub>3</sub> solutions, and water (for constant total volume) taken in separate boiling tubes were thermally equilibrated at 303 K. The reaction was initiated by rapid addition of measured amount of BAT to the mixture and was shaken intermittently for uniform concentration. The progress of the reaction was monitored by iodometric estimation of unreacted BAT in a measured aliquot (5 mL) of the mixture at regular time intervals. The course of the reaction was studied up to 75 to 80% completion. The rate constants were evaluated from the plots of log [BAT] against time. The pseudo-first order rate constants ( $k'$ ) calculated were reproducible within  $\pm 4\%$ .

**2.2. Stoichiometric and Product Analysis.** Varying ratios of levocarnitine and bromamine-T were equilibrated in presence of  $10.0 \times 10^{-3} \text{ mol dm}^{-3}$  HCl and  $6.0 \times 10^{-6} \text{ mol dm}^{-3}$  RuCl<sub>3</sub>, for 24 h at 303 K. Determination of unreacted BAT showed 1 : 1 stoichiometry: (see Scheme 1).

The reduction product of oxidant, *p*-toluenesulphonamide, was extracted with ethyl acetate and detected by thin layer chromatography using petroleum ether-chloroform-1-butanol (2 : 2 : 1 v/v/v) as the solvent and iodine as the reducing agent ( $R_f$  0.88). The reported  $R_f$  value is consistent with given  $R_f$  value in the literature [11]. It was also identified by its melting point 137-138°C (lit m.p. 137-140°C). The oxidation product of levocarnitine, ((R)-(-3-carboxy-2-oxopropyl)trimethylammonium chloride), was detected by spot test and confirmed by IR spectral analysis. IR spectral bands for the product were observed at  $1300 \text{ cm}^{-1}$  (amine salt),  $1390 \text{ cm}^{-1}$  ( $-\text{CH}_3$ ),  $1454 \text{ cm}^{-1}$  ( $-\text{CH}_2$ ),  $1744 \text{ cm}^{-1}$  (C=O),  $1605 \text{ cm}^{-1}$  ( $-\text{COO}^-$ ) and  $1014 \text{ cm}^{-1}$  (aliphatic C-N stretch). It was also observed that there was no further oxidation of these products under the present kinetic conditions.

### 3. Results and Discussion

The oxidation of LC by BAT in the presence of RuCl<sub>3</sub> catalyst has been kinetically investigated at different initial concentrations of the reactants in HCl medium at 303 K.

**3.1. Effect of Reactant Concentrations on the Reaction Rate.** Under pseudo-first order conditions, with the substrate in excess, at constant [LC]<sub>0</sub>, [HCl], [RuCl<sub>3</sub>], and temperature, plots of log [BAT]<sub>0</sub> versus time were linear indicating a first order dependence of the reaction rate on [BAT]<sub>0</sub>. Further, these values are unaffected by a variation of [BAT]<sub>0</sub> (Table 1), confirming the first order dependence on [oxidant]<sub>0</sub>. Under similar experimental conditions, an increase in [LC]<sub>0</sub> increased the  $k'$  values (Table 1). A plot of log  $k'$  versus log [LC] was linear (Figure 1;  $r = 0.997$ ) with a slope of 0.22, showing a fractional-order dependence of the rate on [LC]<sub>0</sub>. The rate of the reaction increases with increase in [HCl] (Table 1) and a

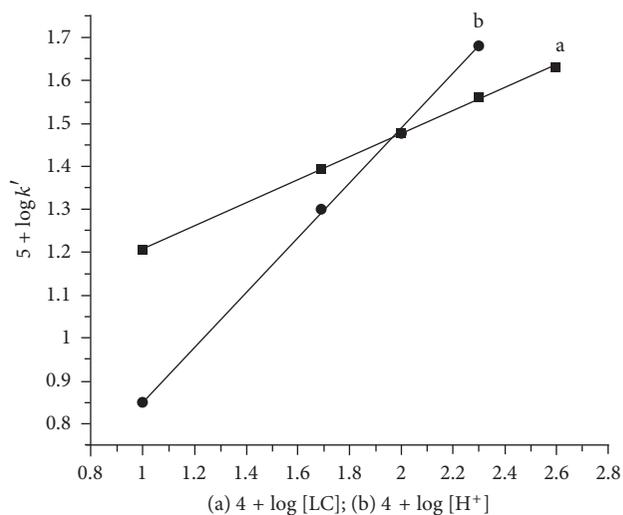


FIGURE 1: Plot of  $5 + \log k'$  versus (a)  $4 + \log [\text{LC}]$ ; (b)  $4 + \log [\text{H}^+]$ .

plot of log  $k'$  versus log [H<sup>+</sup>] was linear (Figure 1;  $r = 0.999$ ) with a slope of 0.62 indicating a fractional-order dependence of rate on [HCl].

**3.2. Effect of Catalyst on the Reaction Rate and Catalytic Activity.** The reaction rate increased with increase in [Ru(III)] (Table 1). A plot of log  $k'$  versus log [Ru(III)] was linear (Figure 2) having a slope of 0.39, indicating a fractional-order dependence on [Ru(III)]. Catalytic constant values were calculated [12] at different temperatures using the relationship between catalyzed and uncatalyzed rate constants:

$$k_1 = k_0 + K_c [\text{Ru(III)}]^x, \quad (1)$$

where  $k_1$  is the observed rate constant in presence of Ru(III),  $k_0$  is the rate constant in absence of catalyst,  $K_c$  is the catalytic constant, and  $x$  is the order of the reaction with respect to Ru(III). Plot of log  $K_c$  versus  $1/T$  was linear and thermodynamical parameters were calculated with respect to the catalyst. The data are summarized in Table 2.

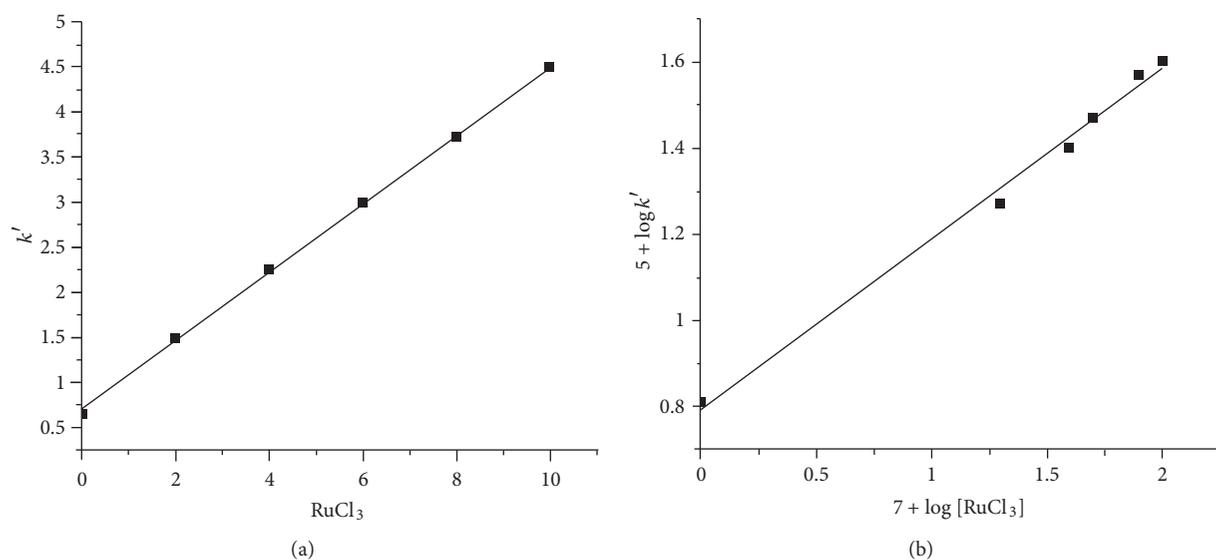
**3.3. Effect of Halide Ions on the Reaction Rate.** At constant [H<sup>+</sup>], addition of NaCl resulted in positive effect on the rate of the reaction (Table 3). Plots of log  $k'$  versus log [Cl<sup>-</sup>] were linear with a positive fractional slope (0.28). Addition of NaBr showed negligible effect on the rate of the reaction.

**3.4. Effect of Added *p*-Toluenesulphonamide on the Rate.** Addition of reduction product of the oxidant, *p*-toluenesulphonamide had a retardation effect on the reaction rate (Table 3). A plot of log  $k'$  versus log [PTS] was linear with negative fractional slope (-0.45), indicating a negative fractional-order dependence on [PTS] and thus suggesting that TsNH<sub>2</sub> is involved in a pre-equilibrium to the rate determining step.

**3.5. Effect of Ionic Strength and Dielectric Permittivity on the Rate.** Variation of ionic strength of the medium using

TABLE 1: Effect of varying concentrations of oxidant, substrate, acid and Ru(III) on the reaction rate at 303 K.

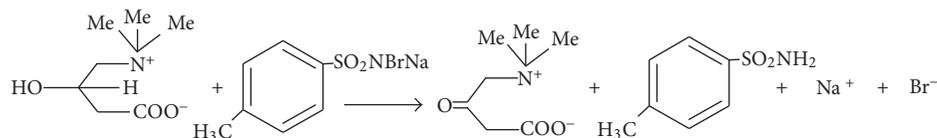
$10^4$ [BAT] (mol dm <sup>-3</sup> )	$10^3$ [LC] (mol dm <sup>-3</sup> )	$10^3$ [HCl] (mol dm <sup>-3</sup> )	$10^6$ [RuCl <sub>3</sub> ] (mol dm <sup>-3</sup> )	$k' 10^4$ (s <sup>-1</sup> )
5.0	10.0	10.0	6.0	3.02
10.0	10.0	10.0	6.0	3.00
20.0	10.0	10.0	6.0	3.10
10.0	1.0	10.0	6.0	1.60
10.0	5.0	10.0	6.0	2.47
10.0	10.0	10.0	6.0	3.00
10.0	20.0	10.0	6.0	3.63
10.0	30.0	10.0	6.0	4.26
10.0	10.0	1.0	6.0	0.70
10.0	10.0	5.0	6.0	2.01
10.0	10.0	10.0	6.0	3.02
10.0	10.0	20.0	6.0	4.80
10.0	10.0	10.0	0.0	0.65
10.0	10.0	10.0	2.0	1.49
10.0	10.0	10.0	4.0	2.25
10.0	10.0	10.0	6.0	3.00
10.0	10.0	10.0	8.0	3.72
10.0	10.0	10.0	10.0	4.50

FIGURE 2: (i) Plot of  $k'$  versus  $[\text{RuCl}_3]$ , (ii) Plot of  $5 + \log k'$  versus  $7 + \log [\text{RuCl}_3]$ .

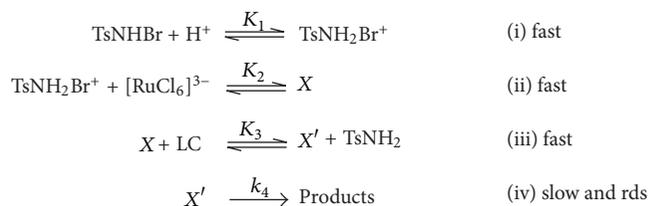
$\text{NaClO}_4$  ( $1.0 \times 10^{-3}$  mol dm<sup>-3</sup> to  $10.0 \times 10^{-3}$  mol dm<sup>-3</sup>) solution did not affect the rate of the reaction. The dielectric permittivity of the medium was varied by adding different proportions of methanol to the reaction mixture. The rate of the reaction increased with increase in methanol content (Table 4). The plot of  $\log k'$  versus  $1/D$ , where  $D$  is the dielectric permittivity of the medium ( $D$  values are taken from the literature [13]), gave a straight line with a positive slope. Blank experiments with methanol indicated that oxidation

of methanol by BAT was negligible under the experimental conditions employed.

**3.6. Effect of Temperature on the Reaction Rate.** The reaction was studied at different temperatures and from the linear Arrhenius plot of  $\log k'$  versus  $1/T$  (Figure 3;  $r = 0.998$ ), values of activation parameters have been computed. These data are presented in Table 5.



SCHEME 1



SCHEME 2

TABLE 2: Catalytic constants at different temperatures.

Temperature K	$10^4 k' \text{ (s}^{-1}\text{)}$		$10^{-2} k_c \text{ (s}^{-1}\text{)}$ w.r.t. catalyst
	Ru(III) catalysed	Uncatalysed	
293	1.82	0.48	1.40
303	3.00	0.65	2.58
313	4.62	1.23	3.68
323	7.30	3.16	4.50

Activation parameters w.r.t. catalyst

$$E_a \text{ (kJ mol}^{-1}\text{)} = 24.8$$

$$\Delta H^\ddagger \text{ (kJ mol}^{-1}\text{)} = 22.28 \pm 0.07$$

$$\Delta S^\ddagger \text{ (J mol}^{-1}\text{)} = -92.97 \text{ J mol}^{-1} \pm 0.29$$

$$\Delta G^\ddagger \text{ (kJ mol}^{-1}\text{)} = 50.449 \pm 0.62$$

TABLE 3: Effect of varying concentrations of NaCl and PTS on the reaction rate.

$10^3 \text{ [conc] Mol dm}^{-3}$	$k' \cdot 10^4$	
	NaCl	PTS
1.0	3.96	2.77
5.0	6.13	1.43
10.0	7.50	1.0
20.0	9.13	0.71

$[\text{BAT}]_0 = 10.0 \times 10^{-4} \text{ mol dm}^{-3}$ ;  $[\text{LC}] = 10.0 \times 10^{-3} \text{ mol dm}^{-3}$ ;  $[\text{HCl}] = 10.0 \times 10^{-3} \text{ mol dm}^{-3}$ ;  $[\text{RuCl}_3] = 6.0 \times 10^{-6} \text{ mol dm}^{-3}$ ;  $T = 303 \text{ K}$ .

3.7. *Test for Free Radicals.* Addition of acrylamide to the reaction mixtures did not initiate polymerization which indicates the absence of free radical species.

Bromamine-T ( $\text{TsNBrNa}$ ,  $\text{Ts} = \text{p-CH}_3\text{C}_6\text{H}_4\text{SO}_2^-$ ) like chloramine-T behaves as a strong electrolyte [14, 15] in aqueous solutions and in acid medium forms different types of reactive species such as  $\text{TsNHBr}$ ,  $\text{TsNBr}_2$ , and  $\text{HOBr}$ . If  $\text{TsNBr}_2$  were to be the reactive species, the rate law predicts

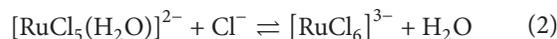
TABLE 4: Effect of varying dielectric constant of the medium on the reaction rate.

Methanol % v/v	$10^2/D$	$10^4 k' \text{ (s}^{-1}\text{)}$
0.0	1.30	3.01
10.0	1.38	3.46
20.0	1.48	4.12
30.0	1.60	4.85

$[\text{BAT}]_0 = 10.0 \times 10^{-4} \text{ mol dm}^{-3}$ ;  $[\text{LC}] = 10.0 \times 10^{-3} \text{ mol dm}^{-3}$ ;  $[\text{HCl}] = 10.0 \times 10^{-3} \text{ mol dm}^{-3}$ ;  $[\text{RuCl}_3] = 6.0 \times 10^{-6} \text{ mol dm}^{-3}$ ;  $T = 303 \text{ K}$ .

a second order dependence of rate on  $[\text{BAT}]_0$  which is contrary to the experimental observations. The rate increases with increase in  $[\text{H}^+]$  but is retarded by the added PTS. Further, it is well known that with aqueous haloamine solutions,  $\text{TsNHBr}$  is the likely oxidizing species in acid medium. Protonation of monohalamines at pH 2 has been reported [16, 17] and in the present case, the fractional-order dependence on  $[\text{H}^+]$  indicates that the protonation of  $\text{TsNHBr}$  results in the formation of  $\text{TsNH}_2\text{Br}^+$  which is likely to be the active oxidizing species involved in the mechanism.

$\text{RuCl}_3$  is also known to exist in solution in various aquaforms. UV spectral studies of aqueous ruthenium(III) complexes have shown that the octahedral complex species such as  $[\text{RuCl}_5(\text{H}_2\text{O})]^{2-}$ ,  $[\text{RuCl}_4(\text{H}_2\text{O})_2]^-$ ,  $[\text{RuCl}_3(\text{H}_2\text{O})_3]$ ,  $[\text{RuCl}_2(\text{H}_2\text{O})_4]^+$ , and  $[\text{RuCl}(\text{H}_2\text{O})_5]^{2+}$  may not exist in aqueous solution of  $\text{RuCl}_3$  [18, 19]. Other studies [20–22] have shown that in acid medium the following equilibrium exists for  $\text{RuCl}_3$ :



In the present study, positive effect with respect to  $\text{Cl}^-$  suggests that the following equilibrium is shifted to the right in acidic ruthenium (III) chloride solution [12, 23]. It may, therefore, be assumed that  $[\text{RuCl}_6]^{3-}$  is the reactive catalysing species in the present case. Ultraviolet spectral measurements showed that  $\text{Ru(III)}$  and  $\text{BAT}$  solutions exhibit absorption

TABLE 5: Effect of temperature on the reaction rate and activation parameters.

Temperature (K)	$10^4 k'$ ( $s^{-1}$ )	$10^4 k_4$ ( $s^{-1}$ )	Active parameters	
			Parameter	Value
293	1.82	(2.63)	$E_a$ ( $\text{kJ mol}^{-1}$ )	35.90 (41.10)
303	3.00	(4.30)	$\Delta H$ ( $\text{kJ mol}^{-1}$ )	33.38 (38.50)
313	4.62	(7.14)	$\Delta G^\ddagger$ ( $\text{kJ mol}^{-1}$ )	94.82 (93.95)
323	7.30	(12.58)	$\Delta S^\ddagger$ ( $\text{J K}^{-1} \text{mol}^{-1}$ )	-202.79 (-182.74)

Values in parenthesis refer to the slow and rate limiting step.

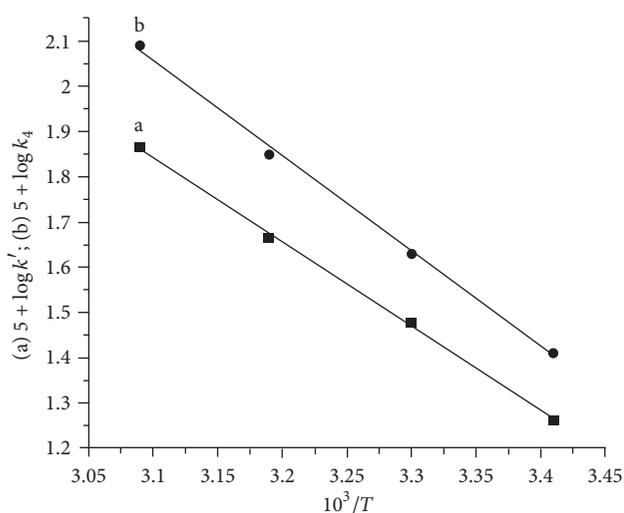
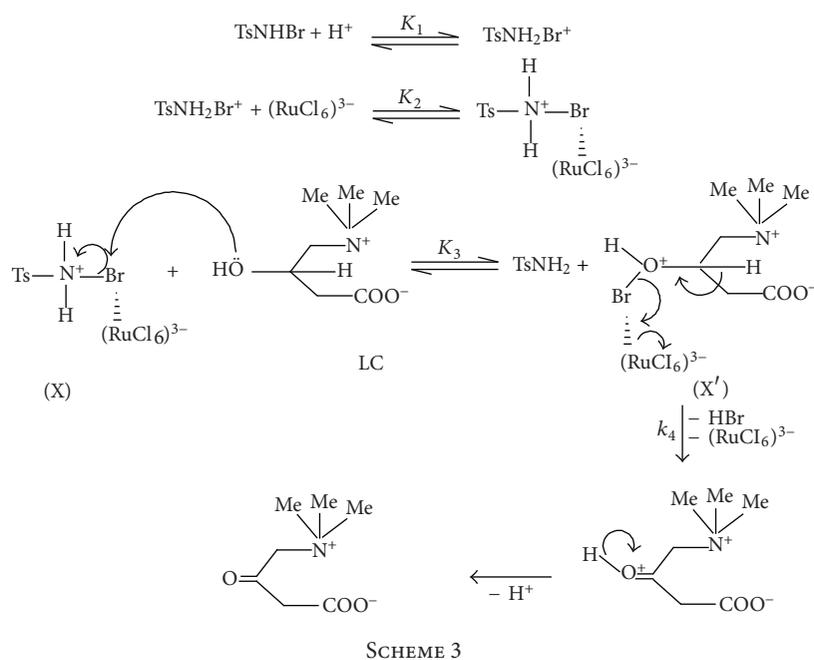


FIGURE 3: Plot of  $10^3/T$  versus (a)  $5 + \log k'$ ; (b)  $5 + \log k_4$ .

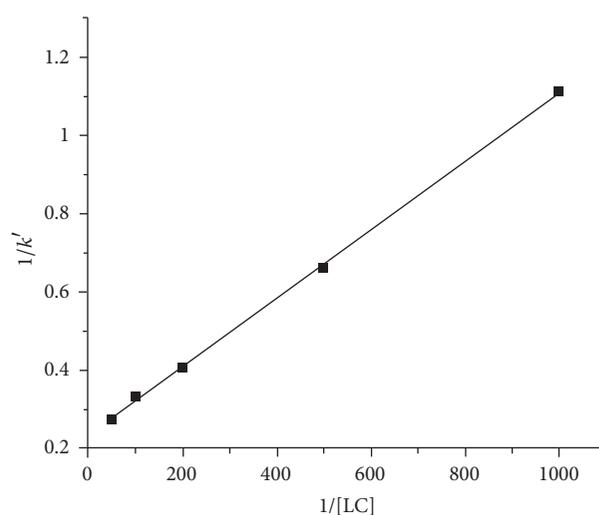


FIGURE 4: Double reciprocal plot of  $1/[LC]$  versus  $1/k'$ .

bands at 204 nm and 224 nm, respectively, in the presence of  $10.0 \times 10^{-3} \text{ mol dm}^{-3}$  HCl and a mixture of both at 233 nm indicating the formation of complex between BAT and Ru(III) [23].

In Scheme 2, X and X' are the intermediate complex species whose structures are depicted in Scheme 3. A detailed mechanistic interpretation of ruthenium catalyzed LC-BAT reaction in acid medium is presented in Scheme 3. An initial

equilibrium involves protonation of TsNHBr forming the active oxidizing species of BAT,  $\text{TsNH}_2\text{Br}^+$ . This step (i) supports the fractional-order dependence on  $[\text{H}^+]$  which was observed experimentally. In the next step,  $\text{TsNH}_2\text{Br}^+$  coordinates to the metal centre of  $[\text{RuCl}_6]^{3-}$  to form a loosely bound metal ion complex (X). This kind of loose metal ion complex formation has been used as an intermediate in some studies involving Ru(III) catalyst [24]. The metal complex further reacts in a fast step with the substrate to form another intermediate species ( $X'$ ) and also  $\text{TsNH}_2$ . The fractional-order in  $[\text{Ru(III)}]$  and negative fractional-order in  $[\text{TsNH}_2]$

support steps (ii) and (iii), respectively, in the mechanism. Finally,  $X'$  in a slow step rearranges to give the product.

Based on Scheme 2 the total effective concentration of BAT is:

$$[\text{BAT}]_t = [\text{TsNH}_2\text{Br}^+] + [\text{TsNHBr}] + [\text{X}] + [X'] \quad (3)$$

By substituting the values of  $[\text{TsNHBr}]$ ,  $[\text{TsNH}_2\text{Br}^+]$ , and  $[\text{X}]$  from steps (i), (ii), and (iii) of Scheme 2 in (3), we get

$$[X'] = \frac{K_1 K_2 K_3 [\text{BAT}]_t [\text{LC}] [\text{H}^+] [\text{Ru(III)}]}{[\text{TsNH}_2] \{1 + K_1 [\text{H}^+] + K_1 K_2 [\text{H}^+] [\text{Ru(III)}]\} + K_1 K_2 K_3 [\text{LC}] [\text{H}^+] [\text{Ru(III)}]} \quad (4)$$

From the slow and rds of Scheme 2,

$$\text{Rate} = k_4 [X'] \quad (5)$$

Substituting (4) in (5), we can obtain the rate law as:

$$\text{Rate} = \frac{K_1 K_2 K_3 k_4 [\text{BAT}]_t [\text{LC}] [\text{H}^+] [\text{Ru(III)}]}{[\text{TsNH}_2] \{1 + K_1 [\text{H}^+] + K_1 K_2 [\text{H}^+] [\text{Ru(III)}]\} + K_1 K_2 K_3 [\text{LC}] [\text{H}^+] [\text{Ru(III)}]} \quad (6)$$

The rate law (6) is in good agreement with the observed kinetic results. From the intercept of linear double reciprocal plot of  $1/k'$  versus  $1/[\text{LC}]$  (Figure 4), decomposition constant ( $k_4$ ) was calculated. The decomposition constant was found to be  $4.3 \times 10^{-4} \text{ s}^{-1}$ . The reduction product of oxidant, PTS, had a retardation effect on the reaction rate indicating that  $\text{TsNH}_2$  is involved in a pre-equilibrium to the rate determining step. The change in the ionic strength of medium does not alter the rate indicating that nonionic species are involved in the rate limiting step. The effect of varying solvent composition and dielectric constant on the rate has been described in several studies. For the limiting case of zero angle of approach between two dipoles or an ion-dipole system, Amis [25] has shown that a plot of  $\log k'$  versus  $1/D$  is linear. The positive dielectric effect observed in the present studies clearly supports the suggested mechanism. The proposed mechanism is further supported by the moderate values of energy of activation and other activation parameters. The fairly high positive values of free energy of activation and enthalpy of activation indicate that the transition state is highly solvated, while the large negative entropy of activation suggests the formation of rigid associative transition states with less degrees of freedom.

#### 4. Conclusions

Oxidation kinetics of LC with BAT in HCl medium catalysed by  $\text{RuCl}_3$  has been studied at 303 K. The

stoichiometry of the reaction was found to be 1:1. The oxidation product of LC was identified as ((R)-(-3-carboxy-2-oxopropyl)trimethylammonium chloride).  $[\text{RuCl}_6]^{3-}$  and  $\text{TsNH}_2\text{Br}^+$  were assumed to be the active reactive species. Activation parameters were computed. The observed results have been explained by a plausible mechanism and the related rate equation has been deduced.

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