



Kinetic, Mechanistic and Thermodynamic aspects of Lidocaine Oxidation by Chloramine-T in Perchloric Acid medium

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Abstract

The kinetics of lidocaine hydrochloride (LC) oxidation by sodium N-chloro p-toluenesulfonamide (CAT) in perchloric acid medium has been studied at 303K. The reaction stoichiometry was determined and oxidation products were identified. The reaction rate shows a first order dependence on [CAT] and fractional order on [LC] whereas inverse fractional order on $[H^+]$. The products of reaction have no considerable effect on the rate. There is a slight negative effect by the dielectric constant. The rate remains same with the variation in the ionic strength of the medium indicating the involvement of non ionic species in rate determining step. There were no free radicals during the course of reaction. Kinetic runs were performed at different temperatures and thermodynamic parameters were computed. A mechanism consistent with observed parameters is proposed and rate law is derived.

Keywords: Kinetics, chloramine-T, Lidocaine, oxidation, mechanism, stoichiometry.

Introduction

Aryl N-halosulfonamides are used as versatile reagents as they react with variety of functional groups performing a wide range of transformations^{1,2}. They act as mild oxidants in both acid and alkaline solutions due to the presence of strongly polarized N-linked halogen in +1 state. Oxidation kinetics of many organic substrates was studied by aryl N-halosulfonamides. A prominent member of this group Chloramine-T (CAT) is a well known analytical reagent. The kinetic and the mechanistic aspects of many of its reactions are well documented³⁻⁸.

Lidocaine, 2-(diethylamino)-N-(2,6-dimethylphenyl)-acetamide, is a local anesthetic that works by temporarily blocking the pathway of pain messages along nerve fibers. It is used to reduce ventricular arrhythmia associated with myocardial infarction, myocardial infarct size and ischemic myocardial injury⁹⁻¹¹. It shows protective effects in stabilizing membranes by its short-lived free radical scavenger effect. It is more effective than β -carotene, sodium azide and histidine in singlet oxygen quenching¹². It is effectively used as an antihemorrhoid, antitussive and in refractory cases of status epilepticus¹³.

A review of the literature provides information about quantitative determination, biodegradation and mechanism of action of lidocaine drug. Oxidation of lidocaine by mild oxidants has not been reported. In the present communication we are reporting kinetic, mechanistic and thermodynamic aspects of lidocaine oxidation by chloramine-T in $HClO_4$ medium at 303 K.

Material and Methods

Experimental: A solution of the oxidant CAT (E. Merck) in water was standardized by the iodometric method and preserved

in brown bottle to prevent any further deterioration photochemically. Aqueous solution of the substrate LC (Sigma) of required strength was freshly prepared each time. The other reagents used were of analytical grade. Double distilled water was used for the kinetic studies. Concentrated solution of sodium per chlorate was used to maintain ionic strength. Methanol was added to alter the dielectric constant. An excess of LC over CAT was maintained to keep pseudo first-order conditions.

Kinetic measurements: In a glass-stoppered Pyrex boiling tube mixture of required amounts of solutions of LC, $NaClO_4$ and acid was taken. Requisite volume of water was added to keep the total volume constant for all runs and thermostated at 303K. An equilibrated solution of CAT of required amount was added to the mixture and shaken appropriately. The reaction progress was studied iodometrically by the estimation of unreacted CAT in a measured aliquot (5 mL) of the reaction mixture with time up to about two half-lives. The pseudo first-order rate constants calculated from the plots of $\log [CAT]$ against time are reproducible within $\pm 3\%$.

Stoichiometry and product analysis: The kinetic runs performed by keeping excess of LC over CAT in $HClO_4$ at 303K confirm the following stoichiometry as one mole of LC consumed two moles of CAT.



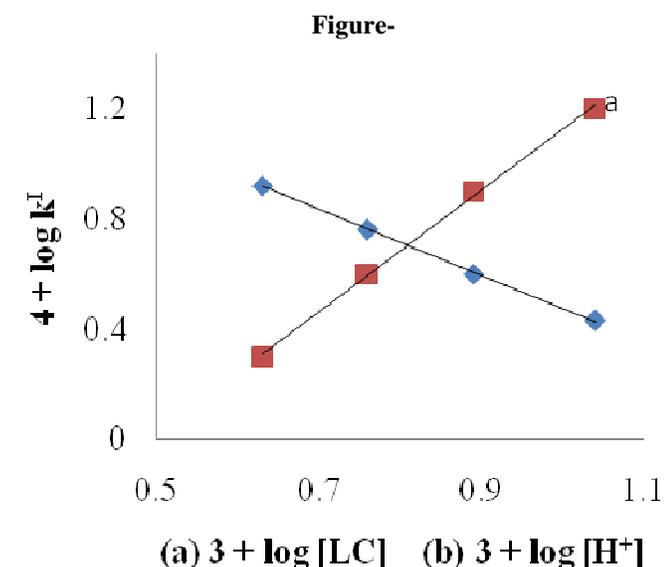
Where, PT = $CH_3C_6H_4$.

The reaction products were extracted with ether. From the ether layer the oxidation product of substrate (2,6-dimethylphenylcarbonyl) formic acid is extracted with

aqueous sodium hydroxide solution and identified by spot test¹⁴. The presence of peptide bond in it is tested by biuret test. Diethyl amine, the other oxidation product is also confirmed by spot tests. The reduction product of CAT, *p*-toluenesulfonamide (PTS), was extracted with ethyl acetate and confirmed by TLC using the system of solvent petroleum ether-chloroform-1-butanol (2:2:1 v/v and the developing reagent iodine (Rf =0.839).

Results and Discussion

Effect of reactants concentration on the rate: Kinetic runs were performed in pseudo-first order conditions ($[LC] \gg [CAT]$) by varied $[CAT]$, at constant $[LC]$, $[HClO_4]$, and Temperature. The linear plots of $\log [CAT]$ versus time indicate a first-order dependence of reaction rate on $[CAT]_0$. From the slopes the pseudo first-order rate constants (k') were calculated (table 1). The unchanged k' values on varying oxidant concentration confirm the first-order dependence of the rate on $[CAT]_0$. Reactions were studied under similar experimental conditions by varying the concentration of $[LC]$. The k' values increased with increase in $[LC]_0$ (table-1). The linear plot of $\log k'$ versus $\log [LC]_0$ (figure-1) with a slope of 0.45 indicate fractional-order dependence on $[LC]_0$.



Effect of (substrate) and (H^+) on rate of reaction

Effect of $[H^+]$ on the rate: Increase in $[H^+]$ using $HClO_4$ results in the decrease of rate (table 1). Linear plot of $\log k'$ versus $\log [H^+]$ (figure 1) with a negative slope of 0.52 indicate an inverse fractional-order dependence of rate on $[H^+]$.

Effect of halide ions on the rate: Reactions were studied by adding $NaCl$ (1×10^{-3} - 10×10^{-3} mol dm^{-3}). The rate remain unchanged with added Cl^- indicate that their effect is not significant on the rate of reaction.

Table-1

Effect of oxidant, substrate and acid concentration on rate

$10^4 [CAT]$ mol dm^{-3}	$10^3 [LC]$ mol dm^{-3}	$10^3 [HClO_4]$ mol dm^{-3}	$k' \cdot 10^4$ S^{-1}
2	4	4	5.74
4	4	4	5.75
8	4	4	5.74
16	4	4	5.75
4	2	4	4.26
4	4	4	5.75
4	8	4	7.76
4	16	4	15.84
4	4	2	8.31
4	4	4	5.75
4	4	8	3.98
4	4	16	2.69

$\mu = 0.5 \text{ mol/dm}^{-3}, T = 303 \text{ K}, 10^2/D = 1.30.$

Effect of ionic strength on the rate: The ionic strength of the medium was varied by the addition of $NaClO_4$ ($0.1 - 1.0$ mol dm^{-3}). The rate of reaction was not changed confirming the involvement of non ionic species in the rate limiting step.

Effect of dielectric constant on the rate: Kinetic runs were performed by varying dielectric constant of the medium adding different proportions (0 - 40 %, v/v) of methanol. Increase in dielectric permittivity (D) of the medium decreased the rate of reaction (table-2). The plot of $\log k'$ versus $1/D$ is linear with a negative slope (figure-2). Under the experimental conditions methanol was ionized to very slight extent ($<1\%$) as confirmed by the blank experiments.

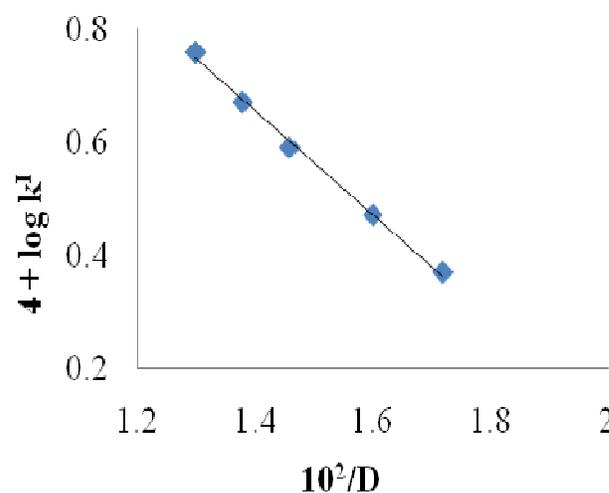


Figure-2

Effect of dielectric constant of the medium on rate

Effect of the product PTS concentration on the rate: The addition of PTS (1×10^{-3} - 10×10^{-3} mol dm^{-3}), the reduced product of oxidant CAT had no significant effect on the rate. This indicates the non involvement of it in pre-equilibrium step.

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	5.75
10	72.4	1.39	4.57
20	67.4	1.47	3.89
30	62.7	1.60	2.82
40	58.1	1.72	2.34

[CAT] = 4 x 10⁻⁴ mol dm⁻³, [LC] = 4 x 10⁻³ mol dm⁻³, [H⁺] = 4 x 10⁻³ mol dm⁻³, μ = 0.5 mol/dm⁻³, T = 303 K.

Effect of temperature on the rate: The kinetic runs were performed at different temperatures (303–323 K) keeping other experimental conditions constant (table-3). From the linear Arrhenius plot of log k' versus 1/T (figure-3) the activation parameters were computed.

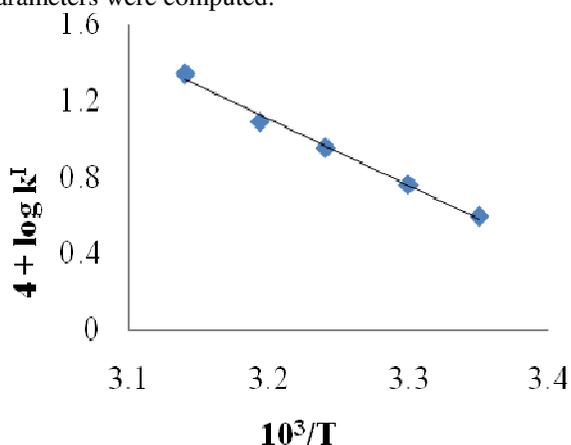


Figure-3
Effect of temperature on rate of reaction

Table-3
Effect of temperature and activation parameters on rate

Temperature (K)	K ¹ 10 ⁴ (S ⁻¹)	Thermodynamic parameter
298	3.89	E _a = 82.39 kJ mol ⁻¹
303	5.75	ΔH [‡] = 79.82 kJ mol ⁻¹
308	8.91	ΔS [‡] = - 43.99 J K ⁻¹ mol ⁻¹
313	12.52	ΔG [‡] = 93.38 kJ mol ⁻¹
318	26.32	-

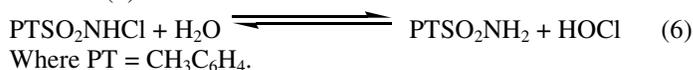
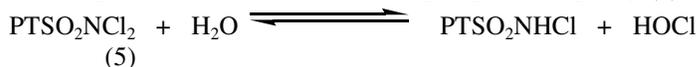
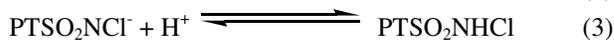
[CAT] = 4 x 10⁻⁴ mol dm⁻³, [LC] = 4 x 10⁻³ mol dm⁻³, [H⁺] = 4 x 10⁻³ mol dm⁻³, μ = 0.5 mol/dm⁻³, 10²/D = 1.30

Test for free radicals: The reaction mixture fails to initiate polymerization when added to aqueous acrylamide. This indicates the absence of any free radical species in the course of reaction.

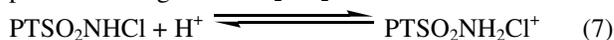
Deduction of rate law and mechanism

Chloramine-T acts as mild oxidant in both acid and alkali solutions with a two electron change to give reduced products.

In aqueous solution it behaves as a strong electrolyte. In aqueous acidic medium it exhibit following equilibria furnishing different ionic species as follows¹⁵⁻¹⁸.

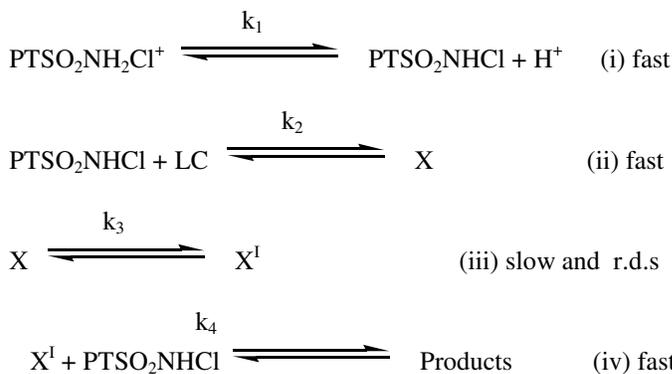


Hence the possible oxidizing species of CAT in aqueous acid mixture are PTSO₂NHCl, PTSO₂NCl₂ and HOCl. The possibility of PTSO₂NCl₂ as reactive species was ruled out as the rate is not second order with respect to [CAT]₀ as from (4). Further the rate does not show first order retardation by the added *p*-toluenesulfonamide. Hence HOCl is not primarily involved in oxidation. Thus PTSO₂NHCl is considered as the active oxidising species. In acid medium (pH<2) PTSO₂NHCl is protonated to give PTSO₂NH₂Cl^{19,20}.

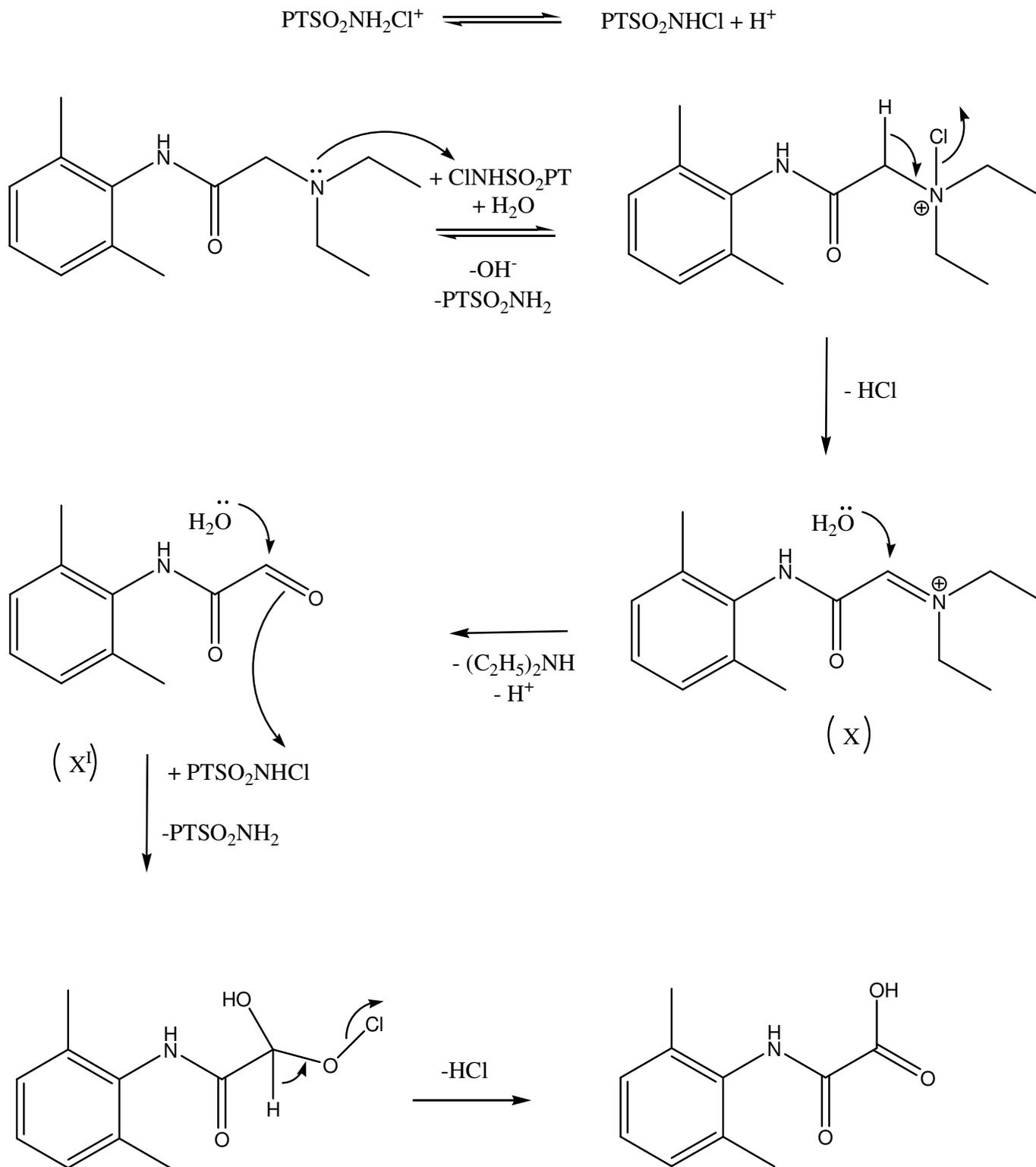


The protonation constant for (8) at 298K is 1.02x10². The rate is retarded by added H⁺ ions confirming the deprotonation of PTSO₂NH₂Cl⁺ leading to the formation of unprotonated active oxidizing species PTSO₂NHCl.

To account for the experimental results of LC oxidation by CAT the following scheme 1 is proposed. Let PTSO₂NHCl represent the active oxidant, LC represent the substrate and X and X^I represent the intermediate complex species. The reaction is initiated through the formation of PTSO₂NHCl which attacks the substrate to give an intermediate complex X which dissociates in the rate determining step to give the complex cation X^I eliminating PTSO₂NH₂. X^I on hydrolysis give X^{II} which reacts with another molecule of PTSO₂NHCl to give products. The detailed plausible reaction mechanism is illustrated in scheme 2.



Scheme-1



Scheme 2

The differential rate equation is $\frac{d[\text{CAT}]}{dt} = k_3 [X]$ (8)

Let $[\text{CAT}]_t$ be the effective total concentration of CAT, then

$$[\text{CAT}]_t = [\text{PTSO}_2\text{NH}_2\text{Cl}^+] + [\text{PTSO}_2\text{NHCl}] + [X] \quad (9)$$

$$[\text{CAT}]_t = ([\text{PTSO}_2\text{NHCl}][\text{H}^+])/k_1 + \frac{K_1}{k_2 [LC]} + [X] \quad (10)$$

On solving for X,

$$[X] = \frac{k_1 k_2 [\text{CAT}]_t [\text{LC}]}{[\text{H}^+] k_2 (1 + k_2 [\text{LC}])} \quad (11)$$

$$\frac{d[\text{CAT}]}{dt} = \frac{k_1 k_2 k_3 [\text{CAT}]_t [\text{LC}]}{[\text{H}^+] + k_1 (1 + k_2 [\text{LC}])} \quad (12)$$

The deduced rate law agrees with the experimental results that a first, fractional and inverse fractional order dependence of reaction rate on $[\text{CAT}]_0$, $[\text{LC}]_0$ and $[\text{H}^+]$ respectively.

Since rate = $k' [\text{CAT}]_0$, from equation (13) we have,

$$k' = \frac{k_1 k_2 k_3 [\text{LC}]}{[\text{H}^+] + k_1 (1 + k_2 [\text{LC}])} \quad (13)$$

$$\frac{1}{k'} = \frac{1}{k_2 k_3 [\text{LC}]} \left\{ \frac{[\text{H}^+]}{k_1} + 1 \right\} + \frac{1}{k_3} \quad (14)$$

Considering equation (13) and 14, plots of $1/k'$ versus $1/[\text{LC}]$ and $1/k'$ versus $[\text{H}^+]$ were linear (Figure 2). From the slopes and intercepts the values of k_1 , k_2 and k_3 were calculated.

Methanol in different proportions (0 - 40 %, v/v) is added to vary dielectric constant of the medium. The negative dielectric effect as seen from the plot of $\log k'$ versus $1/D$ reveals the presence of dipole-dipole interaction in the reaction^{21,23}. Addition of reduction product PTS fails to change the rate indicating its non involvement in pre-equilibrium. The rate remains unchanged on varying ionic strength of the medium indicating the involvement of non-ionic species in the rate limiting step. Halide ions have no significant effect on the reaction rate. Further the computed thermodynamic parameters support the proposed mechanism. A large negative value of entropy of activation and moderate positive values of free energy of activation and enthalpy of activation indicate the formation of properly ordered compact transition state complex having less degrees of freedom.

Conclusion

The CAT-LC redox reaction has been carried out in HClO_4 medium. A 1:2 (equation 1) reaction stoichiometry involving the LC oxidation by CAT has been observed. The products of oxidation are (2,6-dimethylphenylcarbamoyl) formic acid and

diethyl amine. The influence of dielectric constant and halide ions on rate was studied. The thermodynamic parameters, E_a , ΔH^\ddagger , ΔG^\ddagger , and ΔS^\ddagger have been computed from Arrhenius plots. A mechanism consistent with observed parameters has been proposed and rate law was derived.

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