



ELUCIDATION OF KINETIC AND THERMODYNAMIC PARAMETERS OF THE REACTIVITY OF THE HALOGENATION REACTIONS OF REGIO ISOMERS OF METHYL INDOLE IN AQUEOUS MEDIUM BY USING HYDRODYNAMIC VOLTAMMETRY

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ABSTRACT

The study assesses the relative reactivity of the regio isomers of methyl indole in bromination reactions on a quantitative scaffold. The kinetic and thermodynamic data have been obtained for the bromination reactions with the regio isomers of methyl indole by N-Bromo succinimide in the aqueous medium using hydrodynamic voltammetry technique. These reactions follow second order kinetics and are found to be very rapid and the rapidity of the reactions compels the use of the special technique employed herein. The variation in reaction rates with temperature was studied. The specific reaction rates, energies of activation, entropy change and the pre-exponential factor in the reactions were evaluated. The specific reaction rates at 306 K for 1-methyl indole, 2-methyl indole and 3-methyl indole are 2800, 4955 and 1558 $M^{-1}s^{-1}$ respectively. The data has been analyzed to quantitatively ascertain the steric constraints in the dynamics of these reactions.

Keywords: Methyl indole, N-Bromo succinimide, Bromination, Hydrodynamic voltammetry.

1. INTRODUCTION

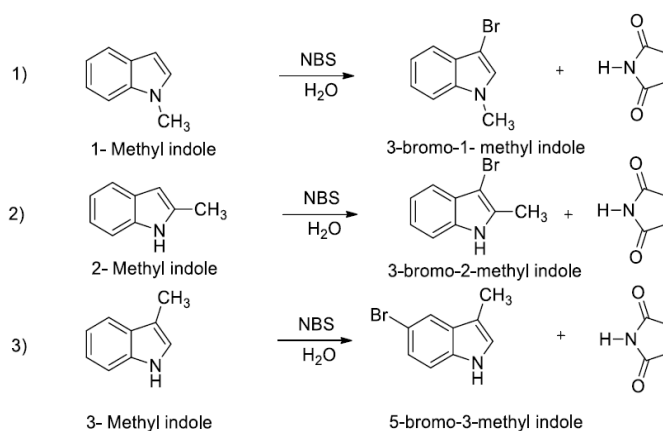
Bromination of aromatic substrate is known to be electrophilic substitution reactions and is rapid in aqueous medium [1]. Rate of electrophilic substitution reaction depends upon the electrophilicity of electrophile, nucleophilicity of the aromatic ring and the nature of the aromatic substrate [2]. As the electrophilicity of the electrophile and nucleophilicity of aromatic ring increase, the rate of the reaction increases. Increase in steric hindrance attenuates the rate of the reaction. Bromo indole is used in Suzuki cross coupling reactions while indoles are ubiquitous species in pharmacodynamics [3, 4].

In aqueous medium, halogenations reaction are very fast and the study of fast reaction kinetics needs specific technique that included temperature jump method, pulse radiolysis technique, competition technique and stopped flow method. In the present study of bromination of regio-isomers of methyl indole in aqueous medium using N-bromosuccinimide, the technique used is hydrodynamic Voltammetry [5, 6].

Among the reactant and product, only N-Bromo succinimide is getting reduced at the electrode surface and its concentration is decreased as reaction proceeds which is measured or monitored by measuring the

diffusion current due to it at a rotations of rotating platinum electrode about 600 rpm speed. Here we used excess concentration of the KNO_3 which is supporting electrolyte and due to that it provides the linear proportionality of the diffusion current at the RPE in the cell.

The reactions under study can be represented as:



2. MATERIAL AND METHODS

2.1. Chemicals

N-bromosuccinimide-A stock solution of NBS is prepared in double distilled water.

Regio-isomers of methyl indole- Required weight of A.R. grade 1-Methyl indole, 2-Methyl indole, 3-Methyl indole were used to prepare their stock solutions in aqueous medium.

Buffer Solution-Sodium dihydrogen phosphate and disodium hydrogen phosphate each of 0.4 molarity were prepared as buffer solutions.

Potassium Nitrate- A.R. grade Potassium nitrate was used to prepare a stock solution that acted as supporting electrolyte.

2.2. Electrodes

A rotating Platinum electrode fused to a glass tube rotated at 600 rpm with the aid of A.C motor acted as the cathode. Saturated Calomel Electrode acted as Anode.

2.3. Construction of the RPE

The rotating platinum electrode (RPE) consisted of 0.5 mm platinum wire fused to one end of inverted "T" shaped glass tube having 6 mm diameter, such that a centimeter of the platinum wire protruded out. A pulley and a pair of ball-bearings were mounted on the glass tube, having the total length of 32 cm. The ball bearings assembly on which the glass tube containing the platinum electrode mounted was fixed rigidly to a stand. A pulley was connected to a synchronous motor. The radius of the pulley was so adjusted that the electrode rotated at a speed of 600 rpm. Some mercury was kept inside the glass tube and a copper wire was dipped in it for electrical contact. The lower portion of the glass tube

effected a stirring action in the solution when the electrode was rotated. A constant potential of +0.1V versus the saturated calomel electrode (SCE) was applied at the RPE, using a potentiometer.

A galvanometer with a sensitivity of 0.10 nA cm^{-1} provided with a lamp & scale arrangement was used for the measurement of the diffusion current due to iodine in terms of the deflection of the galvanometer light spot. The current passing through the galvanometer was controlled by employing a shunt so that the deflection of the light spot was within scale limit.

2.4. Calibration

The working electrodes -RPE and SCE were dipped in 100 mL of $1.25 \times 10^{-3} \text{ M}$ potassium nitrate, the supporting electrolyte. After applying a potential of +0.1V at the RPE with respect to the SCE, the galvanometer light spot was adjusted to zero deflection on the scale. Replacing the potassium nitrate solution by $1.25 \times 10^{-5} \text{ M}$ NBS solution containing $1.25 \times 10^{-3} \text{ M}$ potassium nitrate, the shunt was adjusted for the galvanometer light spot to be within scale limits. This shunt value was kept constant throughout the experiment. The diffusion current values, in terms of the position of the light spot on the scale was noted for various concentrations of NBS in the concentration range $0.25 \times 10^{-5} \text{ M}$ to $1.25 \times 10^{-5} \text{ M}$.

A plot of diffusion current versus concentration of NBS was drawn for different temperatures. The readings were recorded only after allowing the solutions attain the thermostat temperature at which the kinetic study was to be undertaken.

Table 1: Diffusion current for various concentrations of NBS

[NBS] / 10^{-5} M	Diffusion Current (Id) / nA				
	286 K	291 K	296 K	301 K	306 K
0.25	5.40	5.60	5.70	5.90	6.20
0.50	10.8	11.4	11.3	11.8	12.5
0.75	16.0	16.8	17.0	17.7	18.8
1.00	21.3	22.4	22.6	23.6	25.0
1.25	26.5	28.0	28.2	29.0	31.0

2.5. Kinetic measurements

Fifty (50) mL of $2.5 \times 10^{-5} \text{ M}$ 1-methyl indole and 50 mL of $2.5 \times 10^{-5} \text{ M}$ NBS containing $2.5 \times 10^{-3} \text{ M}$ potassium nitrate were taken in two separate flasks and kept in a thermostat to attain the desired temperature. After the solutions reached the thermostat temperature, they were mixed in the reaction vessel kept in the thermostat. RPE and SCE were dipped in the reaction vessel. The stopwatch was started while the solutions

were mixed. As the reaction proceeded, the decreasing galvanometer deflection was observed at every 5 seconds for about a minute.

The procedures of calibration and kinetic measurements were repeated thrice to ascertain the reproducibility of the reaction which is found to be within an error limit of 0.2 cm.

Similar kinetic study was then carried out by using the other two Regioisomers, 2-Methyl indole and 3-Methyl

indole so as to compare the difference in their reaction rates at varying temperatures. During the kinetic study, from the observed deflections, the concentration of unreacted NBS (a-x) at various instants was determined using the calibration curve (fig. 1).

Were, 'a' is initial concentration of reactants, 'x' is concentration of reacted NBS and 't' is time of reaction.

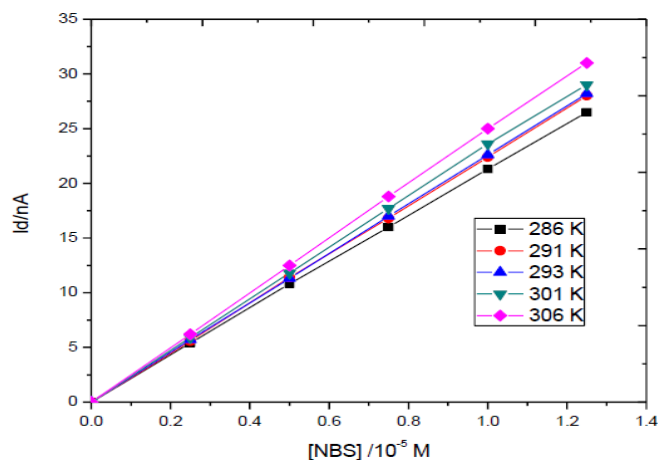


Fig. 1: Calibration of diffusion current

3. RESULTS AND DISCUSSION

From Fig. 2, 3 and 4, a plot of $1/[NBS]$ i.e., $1/(a-x)$ versus 't' was plotted which is linear. Thus, the reaction can conclude to be of second order. The slope of this plot gives the specific reaction rate 'k'. This study was carried out at different temperatures in the range of 286K-306K and the energy of activation of the reactions (E_a) was calculated. Further, the frequency factor (A) and entropy change (ΔS) for the reactions were also evaluated.

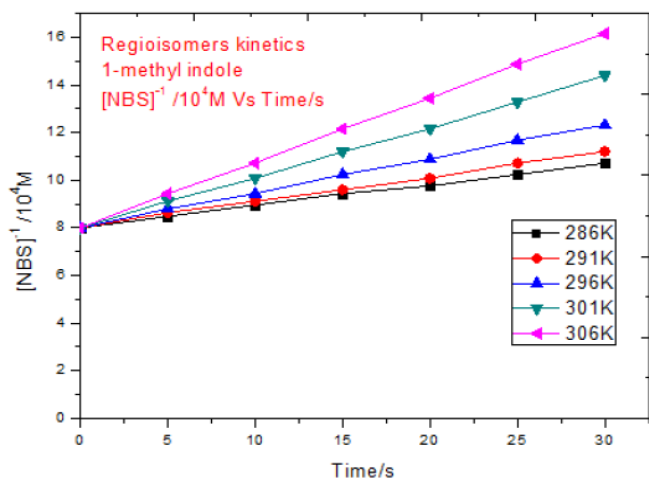


Fig. 2: Kinetics of bromination of 1-Methyl Indole in KNO_3

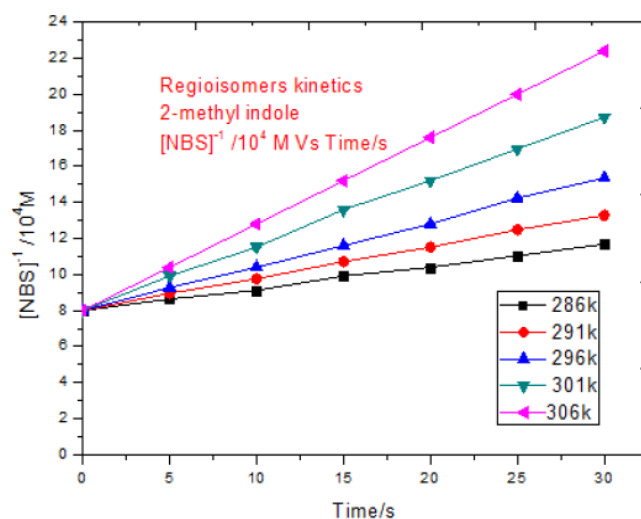


Fig. 3: Kinetics of bromination of 2-Methyl Indole in KNO_3

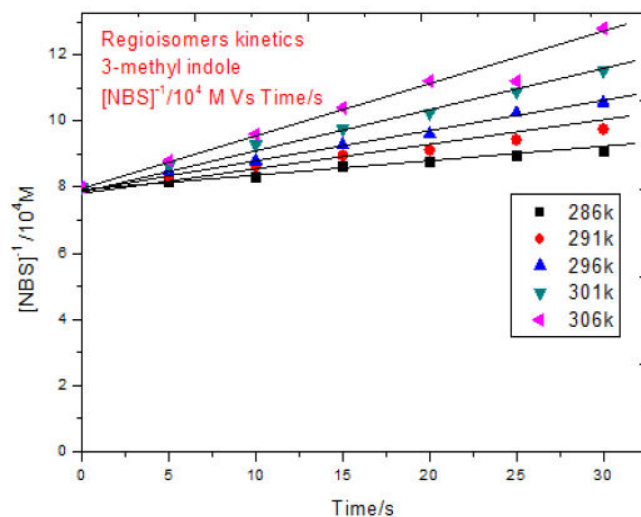


Fig. 4: Kinetics of bromination of 3-Methyl Indole in KNO_3

In the comparative kinetic study of the bromination reaction of the three regio-isomers of Methyl indole, the reactivity order is found to be 3-Methyl indole < 1-Methyl indole < 2-Methyl indole.

In 2-methyl indole donating resonance effect of N heteroatom as well as the donating inductive effect of methyl group together activates position 3 of the 5-membered heterocyclic ring. Hence the rate of bromination of 2-methyl indole is the fastest among the three regioisomers. The reaction is very rapid and has a specific reaction rate of $4955 \text{ M}^{-1}\text{s}^{-1}$ at 306 K.

In 1-methyl indole only donating resonance effect of the tertiary N atom of the heterocycle is observed which activates the third position of the heterocyclic ring and

thus has the specific reaction rate of $2800\text{M}^{-1}\text{s}^{-1}$ at 306K . In 3-methyl indole position 3 of the fused pyrrole ring of indole is blocked by the methyl group and hence substitution occurs at the fifth position in the fused benzene ring of indole. During substitution aromaticity of the fused benzene ring is remarkably reduced and the specific reaction rate of bromination of 3-methyl indole is the slowest among all the regioisomers which is $1558\text{M}^{-1}\text{s}^{-1}$ at 306K .

Thus, the specific reaction rates for the bromination of the regioisomers of methyl indole by NBS in aqueous medium determined in this study assess the steric constraints in the dynamics of these reactions and consequently estimate the relative reactivity of the regioisomers on a quantitative scaffold [7, 8].

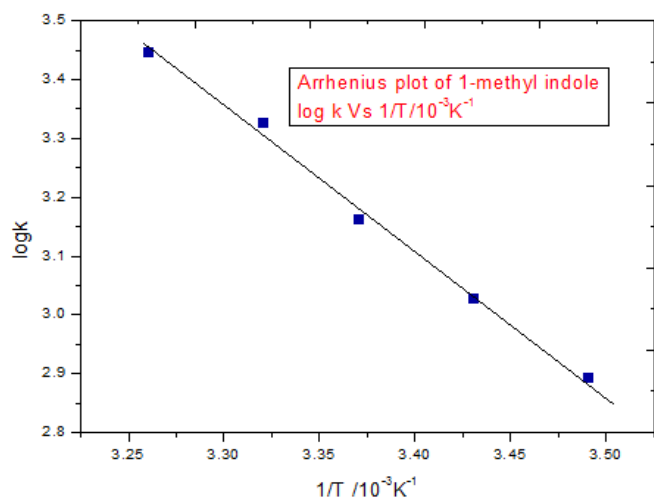


Fig. 5(a): Arrhenius plot of 1-methyl indole

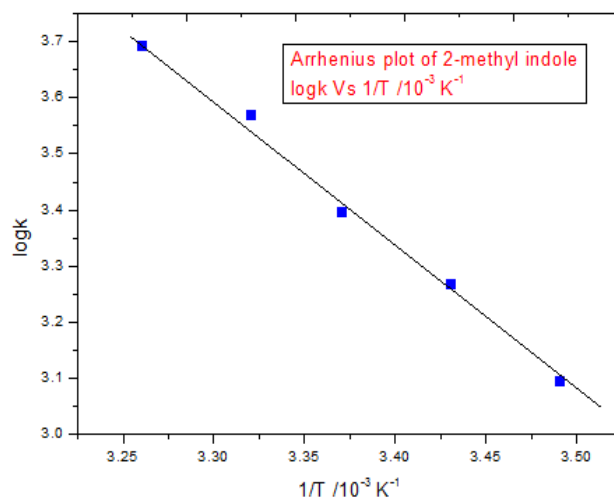


Fig. 5(b): Arrhenius plot of 2-methyl indole

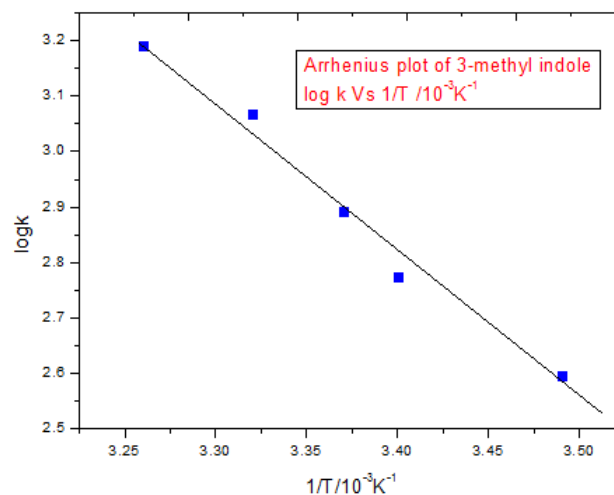


Fig. 5(c): Arrhenius plot of 3-methyl indole

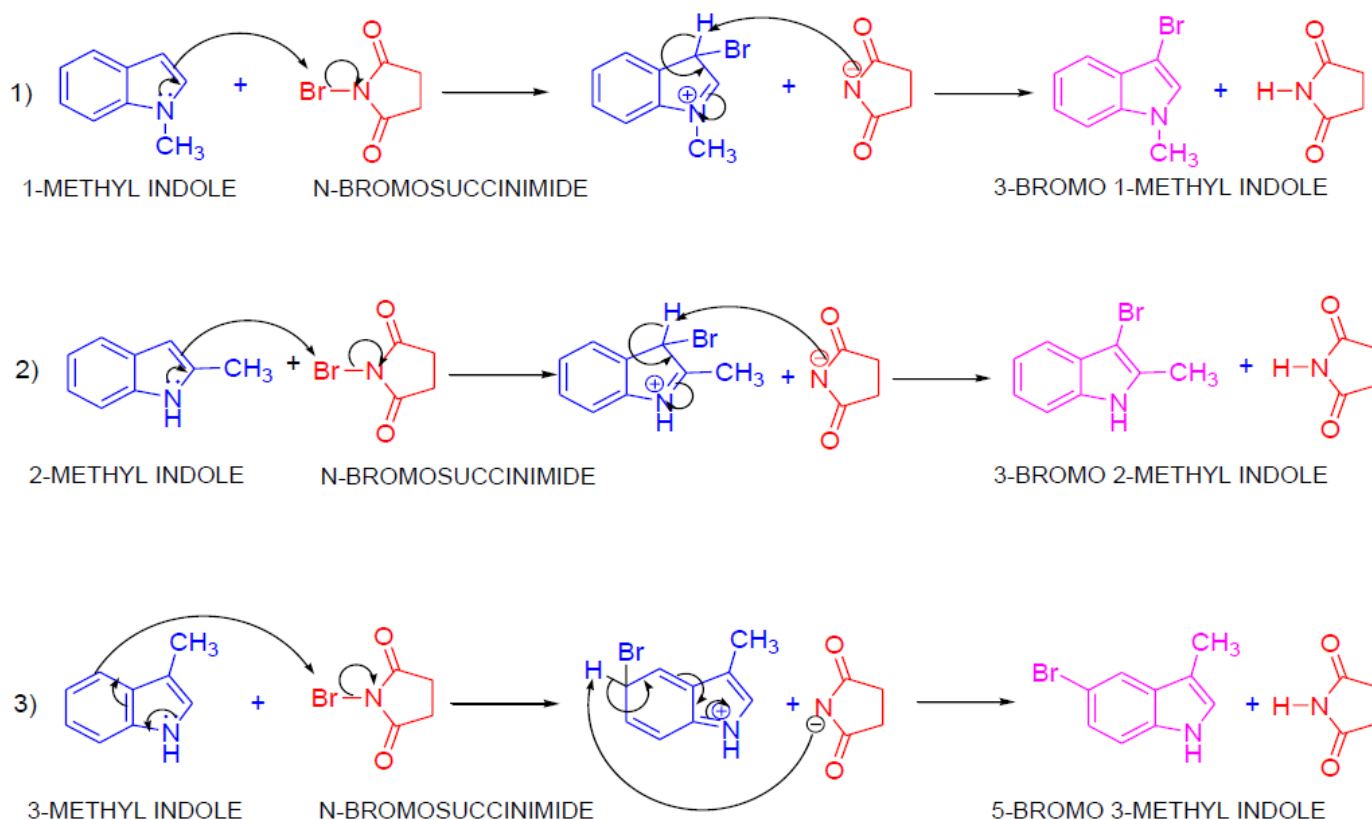
Table 2: The Variation of specific reaction rates of bromination of isomers of Methyl indole with temperature

Temp/K	$T^{-1}/10^{-3}\text{K}^{-1}$	1-Methyl indole		2-Methyl indole		3-Methyl indole	
		$k / \text{M}^{-1}\text{s}^{-1}$	$\log k$	$k / \text{M}^{-1}\text{s}^{-1}$	$\log k$	$k / \text{M}^{-1}\text{s}^{-1}$	$\log k$
286	3.496	882.9	2.8937	1250.12	3.0969	394.50	2.5960
291	3.436	1069.3	3.0290	1860.90	3.2697	593.20	2.7732
291	3.378	1458	3.1637	2490.25	3.3962	780.90	2.8925
301	3.330	2130.5	3.3284	3715.80	3.5700	1168.30	3.0675
306	3.279	2800	3.4470	4954.50	3.6949	1557.89	3.1925

Table 3: Kinetics and thermodynamic parameters for bromination of regio-isomers of Methyl-indole

Sr. No.	Parameters	Experimental values		
		1-Methyl indole	2-Methyl indole	3-Methyl indole
1	Specific reaction rate / $\text{M}^{-1}\text{s}^{-1}$	2800	4955	1558
2	Energy of activation / kJ mole^{-1}	46	45	50
3	Frequency factor / $10^{11}\text{M}^{-1}\text{s}^{-1}$	1.90	2.37	5.32
4	Entropy change / $\text{JK}^{-1}\text{mole}^{-1}$	-45	-43	-37

3.1. Mechanisms



4. CONCLUSION

A comparative study of the reactivities of the Regioisomers of methyl indole has been qualitatively speculated hitherto but by direct kinetic measurements yielding quantitative assessment has herein been provided. These reactions being rapid could not be studied by conventional methods, and the use of Hydrodynamic Voltammetry technique helped to monitor the progress of these reactions to evaluate their specific reaction rates. The data obtained in this study is expected to complement those related to the investigation of bromination of other aromatic substances.

Conflict of interest

None declared

5. REFERENCES

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