

Quantitative Structure-Activity Assessment of the Regioisomers of Methyl Indole using Hydrodynamic Voltammetry

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Abstract: The quantitative structure-activity assessment of the three regioisomers of methyl indole using hydrodynamic voltammetry through chlorination kinetics was undertaken to elucidate the regioselective effect of the methyl moiety. The reagent used was N-chlorosuccinimide. The reactions were found to be very rapid and followed second order kinetics. The rapidity of the reactions necessitated the use of the special technique employed herein. The variation in the reaction rates with temperature was studied. The specific reaction rate, energy of activation, entropy change and the pre-exponential factor for each of the three reactions were evaluated. The specific reaction rates at 306 K for 1-methyl indole, 2-methyl indole and 3-methyl indole were found to be $68.8 \text{ M}^{-1}\text{s}^{-1}$, $460 \text{ M}^{-1}\text{s}^{-1}$ and $50 \text{ M}^{-1}\text{s}^{-1}$ respectively. These kinetic and related thermodynamic data obtained for the three regioisomers of methyl indole were found to be concomitant with the ease of the reaction dynamics considering the regioselectivity of the methyl moiety on indole.

Keywords: Methyl indole, N-chlorosuccinimide, Regioselectivity, Rapid kinetics, Voltammetry

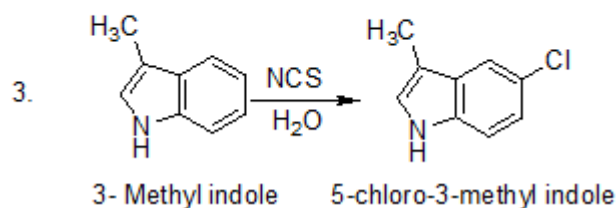
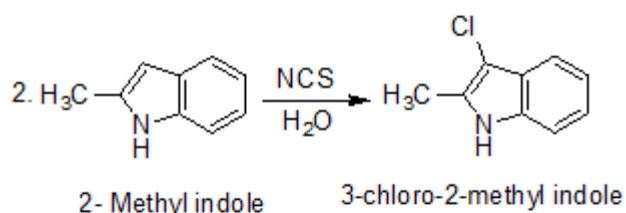
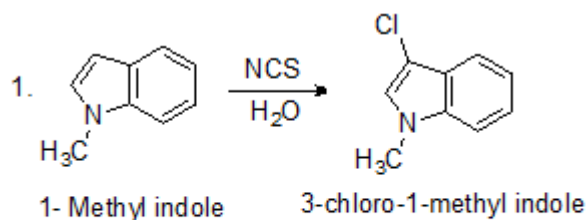
1. Introduction

Indoles are bicyclic heterocycles in which a pyrrole ring is fused to a benzene ring. The two rings share a double bond. The ubiquitous nature of the indole nucleus in a host of bio-active compounds stems from its role as a significant pharmacophore. Indole derivatives like strychnine, imidazole and isatin oxime have significant applications in pharmacodynamics. Chlorinated indole-3-acetic acid is known as a potential anti-cancer drug [1]. We have herein studied the regioselective effect of the methyl group on the reactivity of the three isomers of methyl indole in a quantitative manner through investigation of chlorination kinetics in aqueous solution using N-chlorosuccinimide (NCS).

Chlorination of aromatic substrate are known to be electrophilic substitution reactions, the rates of which depend upon the electrophilicity of electrophile and nucleophilicity of the substrate. As the electrophilicity of the electrophile and nucleophilicity of aromatic ring increase, the rate of the reaction increases. Increase in steric hindrance attenuates the reaction rate. The substituent regioselectivity too needs to be delved into to comprehend the structure-activity correlation more completely [2,3]. Monochloro derivatives of most aromatic substrates are carcinogenic in nature, while di and tri derivatives are known to have several pharmaceutical applications hence their presence in drinking water as a consequence of chlorination is of importance. In aqueous solutions, halogenations of aromatic substrates follow rapid kinetics necessitating the use of special techniques to measure their reaction rates, brominations being the fastest followed by chlorinations[4,5]. These techniques include temperature jump, competition technique, stopped-flow and pulse-radiolysis technique.

Herein the hydrodynamic voltammetry technique has been efficiently adopted to monitor the rate of the fast rapid chlorination of the regioisomers of methyl indole in aqueous

medium using NCS. The rapid decay in concentration of NCS-the only electroreducible species in the reaction is sensed by a microcathode in terms of the diffusion current due to it. The use of a large concentration of the supporting electrolyte KNO_3 ensures linear proportionality of the diffusion current with respect to the concentration of NCS. The reactions under study can be represented as:



2. Experimental

2.1 Chemicals

A.R. grade chemicals were used to prepare the required concentrations of 1-methyl indole, 2-methyl indole, 3-methyl indole, NCS, KNO_3 and buffers in double distilled water.

2.2 Electrodes

A platinum microelectrode was fused to a glass tube and rotated at 600 rpm with the aid of a synchronous A.C. motor (RPC). A saturated calomel electrode (SCE) was the anode.

2.3 Measurement of the diffusion current

A constant potential of + 0.1V versus the saturated calomel electrode (SCE) was applied at the RPC, 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 electrodes RPC and SCE were dipped in 100 cm³ of 2.5 x 10⁻² M potassium nitrate solution. After applying a potential of ± 0.1V at the RPC with respect to the SCE, the galvanometer light spot was adjusted to zero deflection on the scale. The potassium nitrate solution was then replaced with 2.5 x 10⁻⁴ M NCS solution containing 2.5 x 10⁻² M potassium nitrate and the shunt was adjusted for the galvanometer light spot to be within scale limit. This shunt value was kept constant throughout the experiment. The diffusion current value in terms of the position of the light spot on the scale was noted for different known concentrations of NCS from 0.25 x 10⁻⁴ M to 1.25 x 10⁻⁴ M.

A plot of diffusion current versus concentration of NCS was the calibration curve at different temperatures [Fig.1]. The readings were recorded only after allowing the solutions to attain the thermostat temperature at which the kinetic study were to be undertaken.

Table 1: Calibration of diffusion current

[NCS] / 10 ⁻⁴ M	Diffusion Current (Id) / nA				
	286 K	291 K	296 K	301 K	306 K
0.25	3.0	3.3	3.4	3.6	3.8
0.50	6.5	6.6	6.8	7.3	7.6
0.75	9.2	9.8	10.2	10.8	11.3
1.00	12.0	13.1	13.6	14.5	15.2
1.25	15.1	16.5	17.1	18.0	19.0

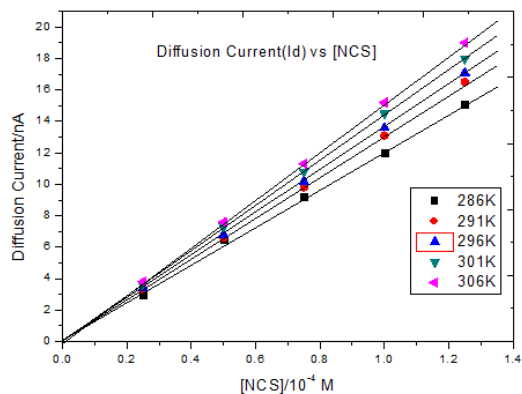


Figure 1: Calibration of diffusion current

2.5 Kinetic Measurements

50 cm³ of 2.5x10⁻⁴ M 1-methyl indole and 50 cm³ of 2.5 x 10⁻⁴ M NCS both containing 2.5 x 10⁻² 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. RPC and SCE were dipped in the reaction vessel. A stopwatch was started while the solutions were mixed. As the reaction proceeded, the decreasing galvanometer deflection due to un-reacted NCS in the reaction was observed at every 10 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.

From the observed deflections, the concentration of un-reacted NCS at various instants was determined using the calibration curve (Fig 1).

Fig 2, the plot of 1/ [NCS] versus time was linear. Thus the reaction was concluded to be of the second order [6,7]. The slope of this plot gave the specific reaction rate 'k'. This study was carried out at different temperatures in the range of 286 K to 306 K and the energy of activation for the reactions (Ea) was calculated. Further, the frequency factor (A) and entropy change (ΔS) for the reaction were also evaluated. Similar kinetic study was then carried out for the other two regioisomers, 2-methyl indole and 3-methyl indole.

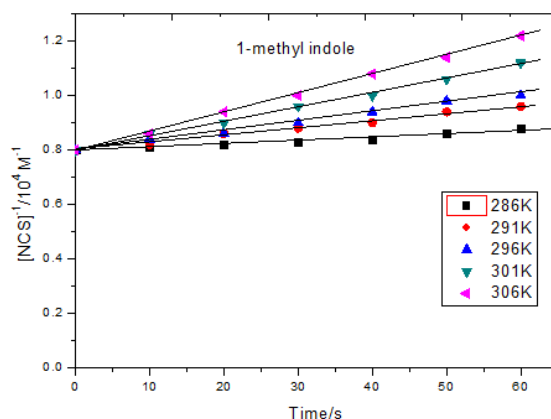


Figure 2: Kinetics of Chlorination of 1- methyl indole

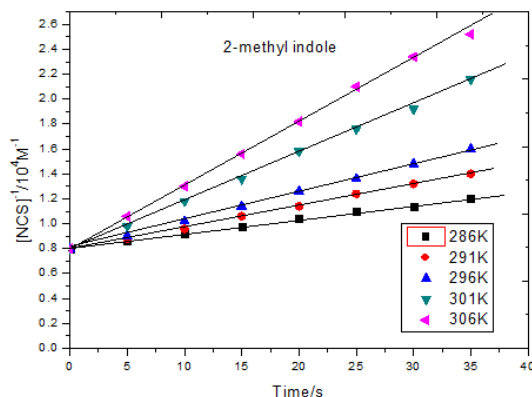


Figure 3: Kinetics of Chlorination of 2- methyl indole

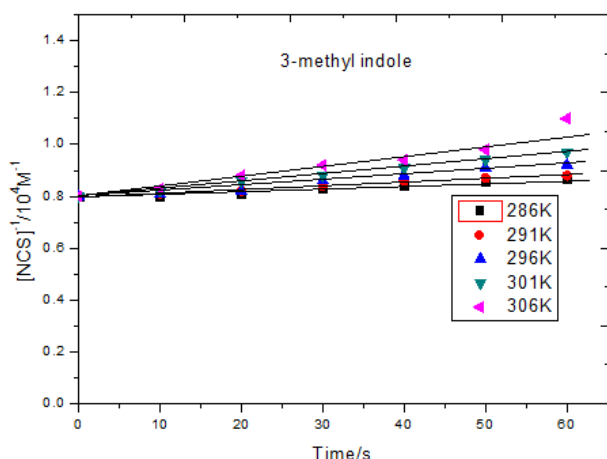


Figure 4: Kinetics of Chlorination of 3- methyl indole

Table 2: The variation of specific reaction rates of chlorination of isomers of methyl indole with temperature

T/K	T ⁻¹ /10 ⁻³ K ⁻¹	1-methyl indole		2-methyl indole		3-methyl indole	
		k/M ⁻¹ s ⁻¹	log k	k/M ⁻¹ s ⁻¹	log k	k/M ⁻¹ s ⁻¹	log k
286	3.496	17.2	1.24	115.0	2.06	12.5	1.09
291	3.436	25.8	1.41	172.5	2.24	18.7	1.27
291	3.378	34.4	1.54	230.0	2.36	25.0	1.39
301	3.330	51.2	1.71	345.0	2.54	37.5	1.57
306	3.279	68.8	1.84	460.0	2.66	50.0	1.69

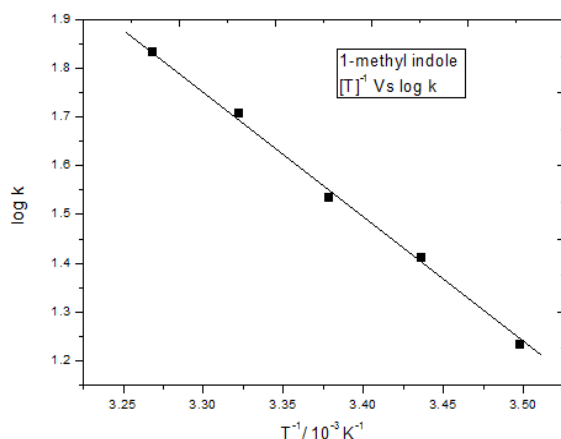


Figure 5 (a):

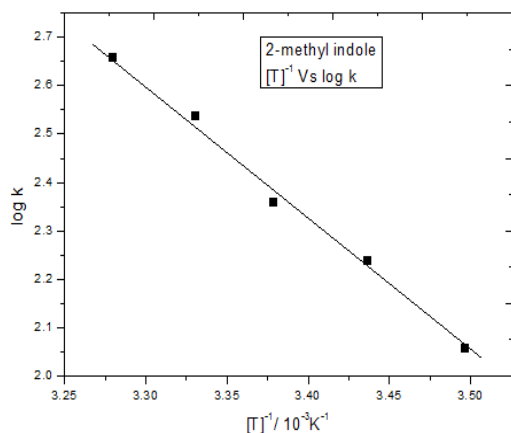


Figure 5 (b):

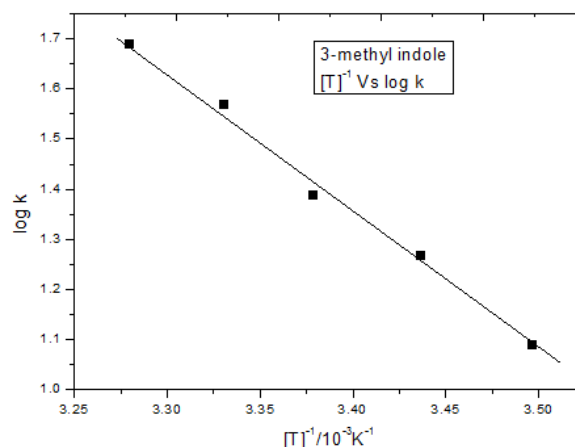


Figure 5 (c):
 Figure: 5(a), 5(b), 5(c): Arrhenius Plots

Table 3: Kinetic and thermodynamic parameters for chlorination of region-isomers of methyl-indole

Parameter	1-methyl indole	2- methyl indole	3-methyl indole
Specific reaction rate /M ⁻¹ s ⁻¹ at 306 K	68.8	460.0	50.0
Energy of activation /kJmol ⁻¹	48	44	49.78
Frequency factor /10 ¹⁰ M ⁻¹ s ⁻¹	1.0717	1.4878	1.569
Entropy of activation /J mol ⁻¹ K ⁻¹	-69.70	-66.93	-66.53

3. Results and Discussion

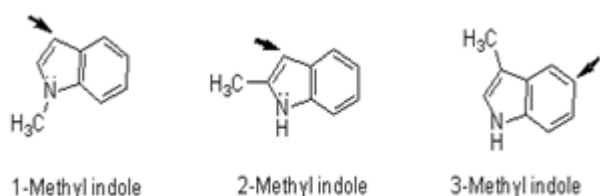
The products of chlorination of 1-methyl indole , 2-methyl indole and 3-methyl indole were found to be 3-chloro- 1-methyl indole , 3-chloro 2-methyl indole and 5-chloro-3-methyl indole, respectively as ascertained from NMR studies.

In the study of the chlorination reactions of the three regio-isomers of methyl indole, the reactivity order was found to be 3-methyl indole < 1-methyl indole < 2-methyl indole.

This is justified on the basis of the stereo-specificity of the compounds. The path of the incoming electrophile Cl⁺ is shown in the figure by arrows.

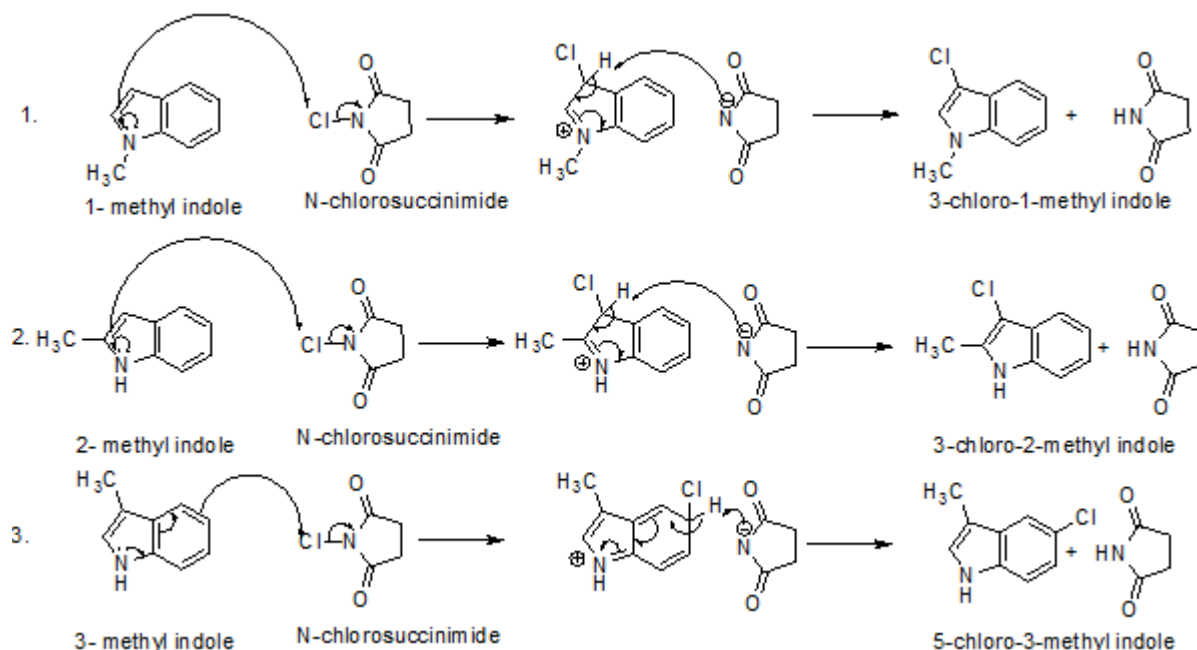
In 1-methyl indole, the presence of methyl group attached to -N provides steric hindrance and makes the lone pair of electrons less available to attack the electrophile. Thus has the least specific reaction rate of 68.80 M⁻¹s⁻¹ at 306 K.. In 3-methyl indole the presence of methyl group at the 3 position causes the electrophile to get attached at position 5. Due to less steric hindrance the reaction was faster as compared to 1-methyl indole, having a specific reaction rate of 50.00 M⁻¹s⁻¹ at 306 K.

In 2-methyl indole, the lone pair of electrons on -N was readily available to attack the electrophile Cl⁺. Position 3 is more conducive to the entry of electrophile due to the combined effect of activating this position by both, the methyl group at position 2 and the nitrogen at position 1. Thus the reaction is rapid and has specific reaction rate of 460.00 M⁻¹s⁻¹ at 306 K.



4. Mechanism

The plausible mechanisms for the three chlorination reactions are suggested as follows.



5. Conclusion

A comparative study of the reactivities of the regio-isomers of methyl indole have 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 facilitated 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 chlorination of other aromatic substrates.

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