Effect of Substituent on the Kinetics of Chlorination of Imidazole by Chlorine in Aqueous Medium

Sandhya Walke[1], Shantaram Bonde[2], Vijay Dangat[3], Ranjana Bhadane[4]

Post Graduate Department of Physical Chemistry, Nowrosjee Wadia College, affiliated to savitribai Phule Pune University, India

Abstract: ***The kinetics of chlorination of imidazole and its regioisomers; 1-methylimidazole, 2-methylimidazole and 4-methylimidazole by molecular chlorine has been carried out in aqueous medium to study the effect of the methyl substituent at various positions in the imidazole ring on the reactivity of the substrate. The reactions follow second order kinetics and since the reactions are rapid, a special technique- hydrodynamic voltammetry was used. The specific reaction rate has been studied at various temperatures to determine the thermodynamic parameters, energy of activation, entropy change, enthalpy of activation and free energy of activation. The specific reaction rate values have been found in the following order: imidazole < 1-methylimidazole < 2-methylimidazole < 4-methylimidazole for their chlorination using molecular chlorine. Stereochemical principles invoked, justified the observed reactivity order for the regioisomers under study. Thus the present work provides the quantitative verification of the relative nucleophilicity of substrates using kinetics as an investigational tool.***

Keywords: Chlorination, Imdazole regioisomers, Kinetics, Hydrodynamic voltammetry

1. Introduction

Imidazole, regioisomers of methylimidazole and related five membered heterocylces are aromatic. Their degree of aromaticity is less than that of six membered ring compounds due to asymmetry in electron density. These heterocycles do not in general conform to aromatic reactitivities speculated for benzene and its derivatives [1]. Imidazole is incorporated into many important biological molecules. The most pervasive is the amino acid“histidine”, which has an imidazole side chain. Histidine is present in many proteins and enzymes and plays a vital part in the structure and binding functions of hemoglobin. Imidazole based hetrocyclic molecules play an important role in various biochemical processes [2]. 1-methylimidazole and related derivatives have been used as mimic aspects of diverse imidazole-based biomolecules. The presence of a halogen allows these reagents to be used as substrates in various coupling reactions. Chloroimidazole is a novel intermediate for the production of anti-hypertensive pharmaceutical agents and herbicidal compounds. Along with these useful applications the chloroimidazoles also have some adverse effects such as they are harmful if swallowed; causes skin and eye irritation. Halogenations of these molecules are very complex and vary considerably depending on the substrates, reagents and reaction conditions. Halogenations of these aromatic substrates in aqueous medium are known to be electrophilic substitution reactions. The kinetics of iodination of 4-methylimidazole and 2- methylimidazole has been reported by earlier investigators [3]. The kinetics of base catalyzed iodination of imidazole and 2-methylimidazole by molecular iodine has also been studied earlier [4]. The present study has been undertaken to investigate the kinetics of chlorination of imidazole and regioisomers of methylimidazole by molecular chlorine in aqueous medium using potassium nitrate as supporting electrolyte. In aqueous medium chlorination of these substrates follow rapid kinetics necessitating a special technique to measure such reaction rates. Some rapid halogenations in aqueous medium have been studied by earlier investigators using hydrodynamic voltammetry in which rotating platinum electrode (RPE) is used [5-10]. It has also been reported that the quantitative assessment of the structure–reactivity correlation in the reaction can be studied using kinetics as an investigatory tool [11]. As the reactions being second order; their half lives are extendable by diluting the solution so that convenient kinetic measurements are possible. Among the reactants and products, chlorine is the only electroreducible species at the rotating platinum cathode [12]. The decaying concentration of chlorine during the course of reaction is measured in terms of diffusion current at the RPE versus saturated calomel electrode, the reference electrode [13]. The purpose of present investigation has been to verify the reactivity of imidazole and its methyl derivatives towards the chlorination using molecular chlorine in aqueous medium.

The study has been carried out at five different temperatures to evaluate the thermodynamic parameters such as energy of activation Ea, Gibbs free energy of activation ΔG*, enthalpy of activation ΔH*, entropy change ΔS* [14]. Hence kinetic data presented here are invoked to justify the relative reactivity of imidazole and regioisomers of methylimidazole in a quantitative manner.

2. Experimental

2.1 Materials

Analytical Reagent (AR) grade samples of imidazole,1-methylimidazole, 4-methylimidazole, 2-methyl imidazole, sodium thiosulphate, potassium nitrate, potassium iodide, bleaching powder, hydrochloric acid and starch were used in the present study to prepare the required stock solutions in double distilled water. For the preparation of stock solution of molecular chlorine the concentrated hydrochloric acid was added drop wise in solid bleaching powder and the liberated gas was bubbled through water to free it from excess HCl. The exact concentration was determined using iodometric titration using starch as an indicator.

2.2 Electrodes

The Rotating Platinum Electrode constructed in which a platinum wire was fused to an inverted ‘T’ shaped glass tube. The electrode rotates at a speed of 600 rpm with aid of motor. The anode was a saturated calomel electrode.

2.3 Calibration of Diffusion Current

The RPE and SCE were dipped in 50 cm^3 100 fold potassium nitrate solution which acts as supporting electrolyte and the galvanometer light spot was adjusted to zero deflection on the scale. The potassium nitrate solution is then replaced by required concentration of chlorine solution. The shunt was adjusted so that the deflection of the galvanometer light spot to be around 35 to 45 cm. The diffusion current values in terms of deflection of light spot on the scale were recorded at various known concentrations of chlorine in the range such as would be occurring in the subsequent kinetic experiments (Table1). The calibration readings are carried out at each temperature. The plot of diffusion current Vs concentration of chlorine was obtained to be linear (Figure1).

Table 1: Calibration of diffusion current in terms of galvanometer deflection at 301.6 K

$[Cl_2]$ /10^{-4}M	Galvanometer deflection/cm
1	7.5
2	15.3
3	22.7
4	31.0
5	38.1

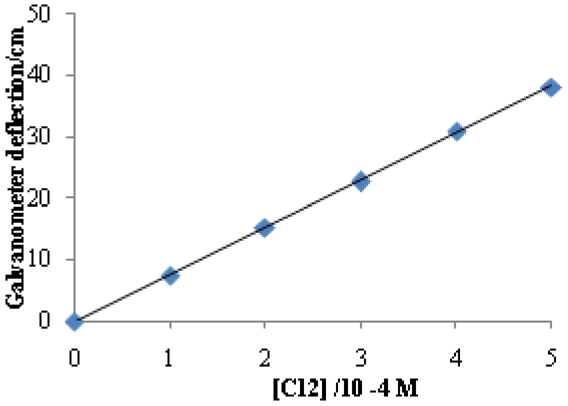


Figure 1: Calibration of diffusion current of molecular chlorine in terms of galvanometer deflection at 301.6 K

2.4 Kinetic Measurements

Equimolar solutions of imidazole and molecular chlorine containing 100 fold of potassium nitrate as supporting electrolyte were kept in the thermostat in separate containers. After attaining the desired temperature they were mixed in the reaction vessel in which the SCE and the RPE were dipped and simultaneously a stopwatch was started. The deflection of light spot of galvanometer was recorded at interval of 10 seconds after mixing. The kinetic measurements were repeated at five different temperatures. With the help of respective calibration curve the concentration of unreacted chlorine at these time intervals were determined. The plot of $[Cl_2]^{-1}$ Vs time was found to be linear (Figure 2). The slope of this plot is the specific reaction rate k at a given temperature. The kinetic measurements were repeated in a similar manner for 1-methylimidazole, 2-methylimidazole and 4-methylimidazole.

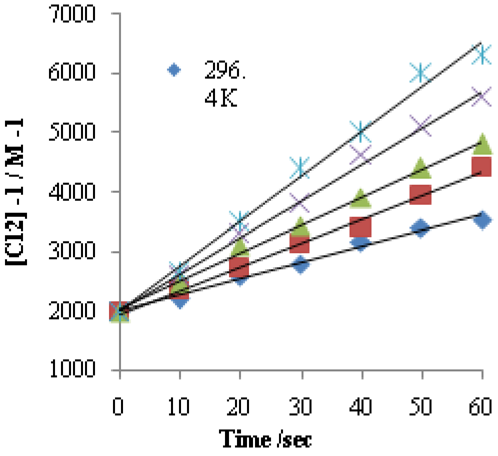


Figure 2: Kinetics of chlorination of 4-methyl imidazole at various temperatures by molecular chlorine

3. Results and Discussion

The kinetics of chlorination of imidazole and its regioisomers by molecular chlorine were observed to follow the second order kinetics, since the plot of $[Cl_2]^{-1}$ Vs time is straight line. The slope of this plot is the specific reaction rate. The study has been carried out at various temperatures the observed values of specific reaction rates are summarized in Table 2. The energy of activation for all the reactions is evaluated from the Arrhenius plot (Figure 3). The other thermodynamic parameters entropy change, enthalpy of activation and free energy of activation also calculated. The results are summarized in Table 3. The kinetic measurements have an error of less than $\pm$2.0% in view of reproducibility of the diffusion current. Chlorine is the sole chlorinating reagent in view of the equilibrium

$$Cl_2 + H_2O \leftrightarrows HOCl + HCl$$

which in aqueous solution is predominantly shifted to the left since, the hydrolysis constant is very low viz. 2.0×10^{-13} [15].

Table 2: Specific reaction rates for chlorination of imidazole and regioisomers by molecular chlorine at various temperatures

T / K	Specific reaction rates / $M^{-1} s^{-1}$			
	Imidazole	1-methyl imidazole	2-methyl imidazole	4-methyl imidazole
296.4	5.98	10.15	16.85	27.45
301.6	9.06	14.87	22.94	39.06
306.6	15.11	19.97	29.67	46.81
311.2	23.42	28.62	36.34	60.91
316.2	30.68	36.59	47.16	74.34

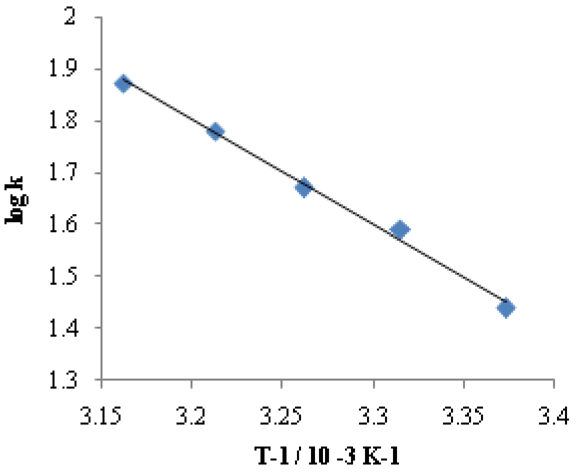


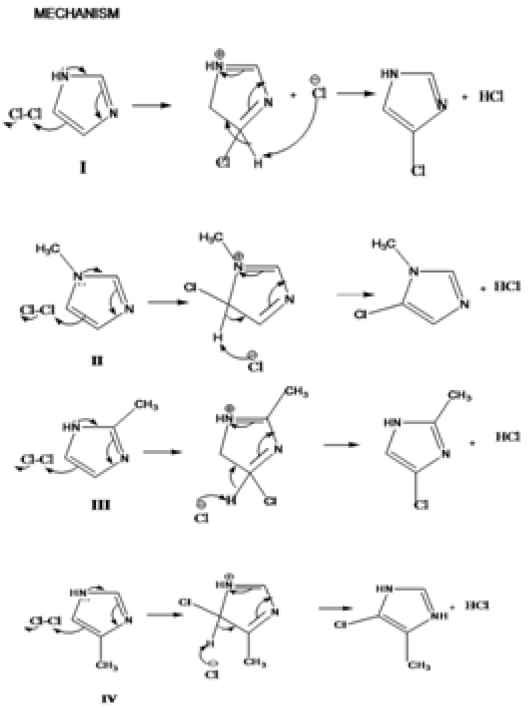
Figure 3: Arrhenius plot for chlorination of 4-methylimidazole

Table 3: Thermodynamics parameters for the chlorination of imidazole and regioisomers by molecular chlorine

Substrates	Thermodynamics parameters			
	Ea / kJ mol^{-1}	ΔH* / kJ mol^{-1}	ΔS* / JK^{-1}	ΔG* / $kJmol^{-1}$
Imidazole	64.33	59.40	-29.55	68.16
1-methyl imidazole	55.56	50.63	-54.71	66.85
2-methyl imidazole	45.70	40.77	-83.75	65.60
4-methyl imidazole	42.12	37.19	-91.78	64.39

The observed values of rate constants for chlorination reaction of substrates under study quantitatively justify the speculations regarding nucleophilicities in the electrophilic substitution reactions. The rate of chlorination of 4–methylimidazole, 2-methylimidazole, 1-methylimidazole and imidazole was found to be in the decreasing order. This order of rate constant observed in the study is explained on stereochemistry principles. The chlorination of imidazole was observed to be slowest. As compared to imidazole **(I)** its methyl regioisomers are observed to undergo chlorination with greater rates. The presence of electron donating methyl group on the ring facilitates the electrophilic substitution reaction. In 1-methylimidazole **(II)** the imidazole ring becomes slightly electron rich due to this electron donating methyl group. But the methyl group is not directly attached to the imidazole ring shows a very minor inductive (+I) effect compared to 2-methylimidazole **(III)** and 4-methylimidazole **(IV)**. Thereby shows slightly greater rate constant as compared to **I** but less than that of **III** and **IV**. As compared to 1-methylimidazole in 2-methylimidazole and 4-methylimidazole the e^- donating methyl group is directly attached to the imidazole ring. The +I effect predominates here shows the increase in reaction rates compared to **I** and **II** for their chlorination. The relatively lower rate of 2-methylimidazole is presumably due to the methyl group in 2-methylimidazole is sandwiched between the two electronegative nitrogen at the one and three positions of imidazole ring, thereby suppressing its electron donating (+I) effect. Also in 2-methylimidazole there is steric hindrance encountered among the methyl and two nitrogen at position one and three which make it relatively less reactive compared to 4-methylimidazole.

The mechanism for the chlorination of the substrates under study can be explained as follows. The π e^- cloud of the substrate ring readily attack the +ve end of the Cl_2 molecule. Subsequently the substrate molecule losses its aromaticity and becomes unstable. The –ve end of the Cl_2 molecule abstracts the proton in the fast step to stabilize the ring in order to re-attribute aromaticity to it. The plausible mechanistic route in these reactions may be shown as follows.



The products of the reactions under study has been confirmed stochiometrically and by recording the ^1H NMR spectra which confirms formation of monochloro derivatives. The results are shown in Figure 4 (a,b,c and d). Figure 4a represents ^1H NMR for monochloro derivative of **I**. H at position one and two shows singlet at 8.4 and 7.3 ppm respectively. And the H at position five gives singlet at 7.2 ppm instead of 7.1 ppm due to chlorination at position four. If chlorination of imidazole takes place at position two, H at four and five position will give doublet of doublet which is absent in this case. Figure 4b shows ^1H NMR spectra for monochloro derivative of **II**. Two singlets are observed at 7.4 and 7.0 ppm for H at position two and four respectively. Methyl protons show chemical shift at 3.6 ppm. Absence of doublet of doublet confirms the substitution at position five and not at two. Figure 4c represents ^1H NMR of chlorination of **III** which shows singlet at 6.9 ppm for H at five position and methyl protons at 2.4 ppm while H at position one is offset proton which confirms monochloro derivative of **III.** In Figure 4d singlet is observed at 7.2 ppm instead of 6.8 ppm which confirms chlorination of **IV** at position five and not at two. Methyl protons at position four shows signal around 2.2 ppm. In all these figures of ^1HNMR spectra other than methyl proton signals, the signals between 1 to 5 ppm indicate the presence of solvent. Thus the ^1H NMR spectra confirms the formation of monochloro derivatives of **I, II, III**, and **IV**.

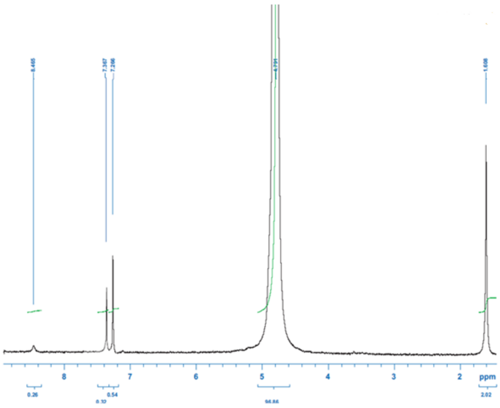


Figure 4a: ^{1}H NMR spectrum recorded for the mono chloro derivative of imidazole **(I)**

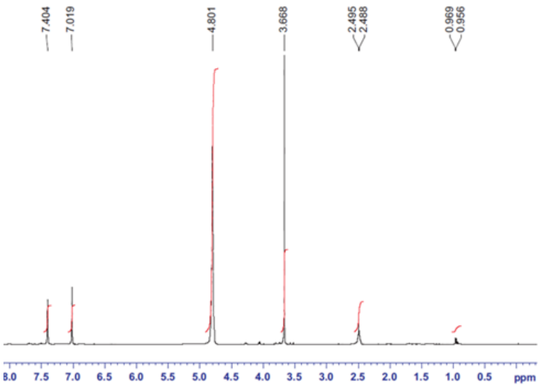


Figure 4b: ^{1}H NMR spectrum recorded for the mono chloro derivative of 1-methylimidazole **(II)**

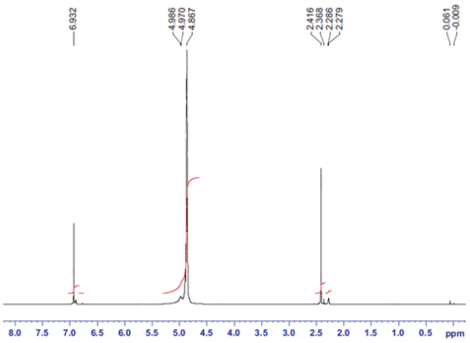


Figure 4c: ^{1}H NMR spectrum recorded for the mono chloro derivative of 2-methylimidazole **(III)**

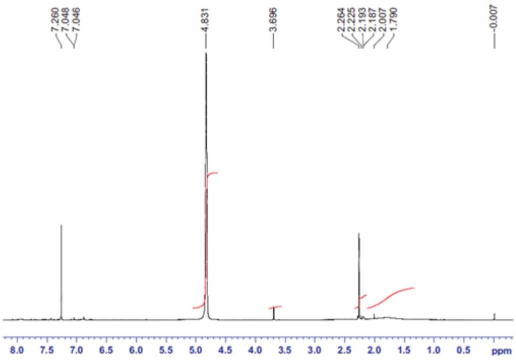


Figure 4d: ^{1}H NMR spectrum recorded for the mono chloro derivative of 4-methylimidazole **(IV)**

4. Conclusion

The chlorination of imidazole, 1-methylimidazole, 2-methylimidazole, 4-methylimidazole by molecular chlorine in aqueous medium follows second order kinetics. The reactions being rapid necessitate a special technique hydrodynamic voltammetry. The five membered rings are less aromatic than six membered rings hence only monochloro product is formed. The nature of products for all reactions was confirmed by recording ^{1}H NMR spectra. The rate constant values are observed in increasing order for the chlorination of imidazole, 1- methylimidazole, 2-methylimidazole and 4-methylimidazole. The relative reactivities of imidazole and its methyl regioisomers are speculated only qualitatively on the basis of stereochemical principle. The quantitative assessment is provided hitherto by the kinetic measurements of chlorination of these isomers.

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Author Profile

Dr. Shantaram L. Bonde, Former Principal, Nowrosjee Wadia College, Pune (India). He is the author of twenty three research papers. His research interests are in the field of rapid kinetics, ionic equilibrium,

Dr. V. T. Dangat, Former Head, Dept. of Chemistry, Nowrosjee Wadia College, Pune (India). He is the author of twenty three research papers with a few citations. His research interests are in the field of rapid kinetics and polarography.

Dr. Mrs. R. P. Bhadane, Associate Professor, Dept. of Chemistry, Nowrosjee Wadia College, Pune (India). She is the author of twenty one research papers. Her research interests are in the field of rapid kinetics and ionic equilibrium.

Sandhya B. Walke, received her M. sc in Physical Chemistry from Nowrosjee Wadia Collge, affiliated to Savitribai Phule Pune University. Currently pursuing Ph.D Degree in the same university.