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QUANTITATIVE ASSESSMENT OF RELATIVE REACTIVITY OF MOLECULAR HALOGENS IN THE KINETICS OF HALOGENATIONS OF 2-METHYLTHIAZOLE IN AQUEOUS MEDIUM USING HYDRODYNAMIC VOLTAMMETRY

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ABSTRACT

The relative reactivity of different halogenating reagents in the electrophilic substitution reactions has been quantitatively investigated using kinetics as an investigational tool. In the present study, the halogenation of 2-methylthiazole in aqueous medium has been studied at 23.5^0C using I_2, Cl_2 and Br_2 as the halogenating reagents. The presence of electron donating methyl group activates the thiazole ring towards the elctrophilic substitution reaction. The reactions follow the second order kinetics. The rapidity of the reactions necessitated the use of a special technique i.e. hydrodynamic voltammetry, to follow the course of the reaction. The extent of reactions was measured by following the decrease of nano diffusion current due to the reduction of halogenating reagents with time using rotating micro platinum cathode. The order of specific reaction rates was observed as $k_{\text{Bromination}} > k_{\text{Clorination}} > k_{\text{Iodination}}$. The kinetic study has also been carried out at different temperatures to determine the various activation parameters. The kinetic data thus invoked justifies the quantitative assessment of the comparative reactivity of these halogenating reagents towards the halogenation of 2-methylthiazole.

Key words: Hydrodynamic voltammetry, Kinetics, Rapid halogenations, 2-Methylthiazole, Relative reactivity.

INTRODUCTION

The halogenations of five membered aromatic heterocycles have been the subject of great interest due to the potential applications of their derivatives[1,2]. The halogenated derivatives of heterocycles such as imidazole, pyrazole and thiazole have numerous applications in various fields[3,4]. The iodo derivatives of these heterocycles are observed to be the valuable precursors for the selective construction of highly functionalized organic molecules of synthetic and biological importance[5]. The presence of a halogen allows the thiazole ring to be used as substrates in various coupling reactions, including Suzuki-Miyaura cross-coupling reactions[6].

The halogenations of these aromatic heterocycles are known to be electrophilic substitution reactions[7]. The substituent can be introduced into thiazole ring but the reactivity towards the electrophilic substitution is observed to be very less in thiazole ring[8]. Earlier study on the kinetics of bromination of thiazole, imidazole and pyrazole in aqueous medium showed that the specific reaction rate is less for

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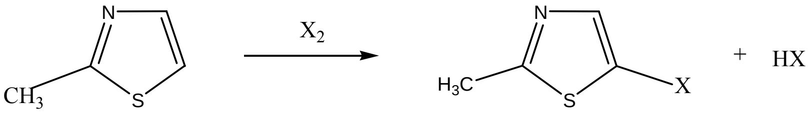
bromination of thiazole than that of bromination of pyrazole and imidazole[9]. The presence of pyridine like nitrogen in the thiazole ring deactivates the ring towards the electrophilic attack. The smoother substitutions in thiazole ring thus require the presence of activating or electron releasing groups. The methylthiazole thus can easily undergo electrophilic substitution reactions as the electron donating methyl group on the ring increases the rate of electrophilic attack. The relative reactivities of halogenating reagents towards the halogenations of heterocycles are of interest in understanding the elctrophilic aromatic substitution reactions. The quantitative data for such reactions have been scanty. We have therefore studied the kinetics of halogenations of 2-methyl thiazole using molecular iodine (I_2), chlorine (Cl_2) and bromine (Br_2) as halogenating reagents. The reactions are carried out in aqueous medium since, in acidic conditions the thiazole nitrogen is protonated and the resulting azolium cation is relatively inert to further attack by positively charged electrophile[10]. The use of aqueous medium, very low concentrations of reactants and the rapidity of the reactions makes the study environmentally friendly[11].

The reactions are of second order and are too rapid to be measured by conventional methods. Various methods can be used to study the kinetics of fast reactions such as temperature jump, stopped flow, pulse radiolysis technique etc.[12] In the present study we have employed the special technique namely, hydrodynamic volatammetry in which rotating micro platinum electrode is used to follow the progress of reactions at various time intervals[13,14]. Some bromination reactions have been studied using rotating platinum electrode (RPE) by Speneer and Bell[15,16]. Since the halogens (X_2) are the only electro reducible species among the reactants and products, their change in concentration during the progress of reaction is measured in terms of nano diffusion current using rotating micro platinum cathode with saturated calomel electrode (SCE), the reference electrode[17]. Diffusion current at RPE is measured in terms of deflection of galvanometer light spot with the help of lamp and scale arrangement, which is calibrated in nano ampere current.

Kinetic study has also been carried out at five different temperatures to evaluate the activation parameters such as frequency factor, energy of activation, enthalpy of activation and entropy change. The data obtained in the kinetic study has been used as an investigational tool that signifies the quantitative assessment of relative reactivity of these three halogenating reagents towards the halogenation of a 2-methylthiazole in an aqueous medium. It is envisaged that the present study will find interest to researchers in the field to use the halogen derivatives for various applications.

The reactions under study are:



($X_2 = I_2$ or Cl_2 or Br_2)

EXPERIMENTAL

Chemicals

2-Methylthiazole, iodine, bromine, sodium thiosulphate, potassium nitrate and potassium iodide of analytical grade were used to prepare the stock solutions of required concentrations.

Chlorine water was prepared by using A. R. grade bleaching powder and the concentrated hydrochloric acid. Concentrated HCl was added drop wise to bleaching powder, liberated Cl_2 gas as per the reaction, was collected in double distilled water. Iodine solution was prepared by dissolving A.R. grade iodine crystals in double distilled water. Solution of iodine was devoid of I^- ions. Liquid bromine was obtained from Sigma-Aldrich, which was dissolved in double distilled water. The stock solutions of these halogenating agents thus prepared were stored in the ground glass stoppered amber color bottles to protect from the sunlight. Prior to the study, every time these solutions were standardized to know the exact concentration by iodometric titration method using starch as an indicator. The standardized solutions of iodine, chlorine and bromine were diluted to get the required concentration of each containing hundred folds of potassium nitrate as the supporting electrolyte. The hundredfold molar concentration of KNO_3 ensures the linear proportionality of the current at the RPE.

$$CaOCl_2 + 2\ HCl \longrightarrow CaCl_2 + H_2O + Cl_2$$

The electrochemical processes involved at the two electrodes are as follows:

$X_2 + 2\ e^{\ominus} \longrightarrow X^{\oplus} + X^{\ominus}$ At the positive electrode, RPE

$2\ Hg + 2\ Cl^- \longrightarrow Hg_2Cl_2 + 2\ e^-$ At the negative electrode, SCE

$X_2 + 2\ Hg + 2\ Cl^- \longrightarrow Hg_2Cl_2 + X^+ + X^-$ Overall reaction

Calibration of diffusion current

The rotating platinum electrode (RPE) and saturated calomel electrode (SCE) were dipped in 50 cm^3 of KNO_3 solution having 100 folds concentration with respect to halogen concentration. The galvanometer light spot was adjusted at zero cm on the scale corresponds to zero nano ampere current at applied potential of 0 Volt. KNO_3 solution was then replaced by 1×10^{-3} M I_2 solution. The maximum nano current due to the reduction of electroactive iodine at the applied potential of 0 volt was obtained by adjusting the galvanometer light spot at the maximum level on the scale with the help of shunt. Keeping shunt position constant throughout the experiment, the diffusion current was then measured at various concentrations of I_2 in the range 0.2×10^{-3} M to 1×10^{-3} M. The plot obtained for the diffusion current vs. the concentration was linear.

Table 1: Calibration of the diffusion current of I_2

$[I_2]$ (10^{-3} M)	**Diffusion current (nA) at various temperatures**				
	291.5 K	**296.5 K**	**301.6 K**	**306.6 K**	**311.4 K**
0.2	7.3	7.7	7.5	10.5	9.9
0.4	14.0	16.4	17.0	19.1	20.2
0.6	21.2	23.0	23.0	25.5	30.2
0.8	28.5	31.5	31.8	35.0	40.1
1.0	35.5	38.0	40.2	45.2	48.4

The similar procedure was repeated for the calibration of diffusion current due to chlorine and bromine.

Kinetic measurements

For the kinetic measurements, 25 cm^3 aliquots of 1×10^{-3} M solution of iodine containing 100 folds potassium nitrate and 25 cm^3 1×10^{-3} M 2-methylthiazole were kept in the thermostat. After attaining the desired temperature the solutions were mixed in the reaction vessel containing the RPE and SCE. The extent of reaction was measured as decrease of nano diffusion current in terms of deflection of galvanometer light spot on a scale at various time intervals at the applied potential of zero volts. The concentration of iodine at various time intervals was obtained from the calibration curve. Since the reaction is of second order, the reciprocal of [I_2] versus time was plotted which was observed to be linear. The kinetics measurements were repeated at five different temperatures.

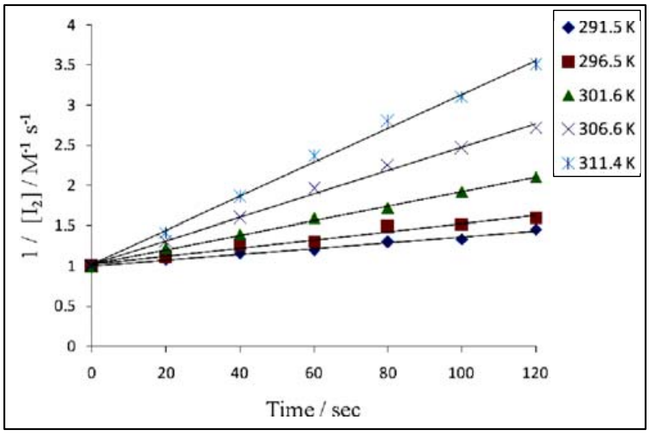


Fig. 1: Kinetics of iodination of 2-methylthiazole by molecular iodine at various temperatures

The reproducibility of results was checked by repetition of measurement of diffusion current, which was found to be within the limits of ± 0.2 cm. The slope of this plot gives specific reaction rate k_2. The kinetics measurements were also repeated at various temperatures for chlorination and bromination of 2-methylthiazole by molecular chlorine and bromine, respectively.

RESULTS AND DISCUSSION

The specific reaction rates have been determined for the halogenation of 2-methylthiazole using hydrodynamic voltammetry technique. The decrease in diffusion current due to the disappearance of halogen concentration, as it gets reduced at the applied potential, was obtained. These diffusion current values give the concentration of halogens remained at various time intervals. Since the reactions are of second order, the plot $[X_2]^{-1}$ versus time was linear, the slope of which gives the specific reaction rate. The values of specific reaction rates at various temperatures were determined for the halogenation of 2-methyl thiazole using molecular halogens X_2 ($X_2 = I_2$, Cl_2, and Br_2), and the results are summarized in the Table 2. The kinetic measurements have an error of not more than ± 2% in view of the reproducibility of the diffusion current measured at the RPE.

Table 2: Variation of specific reaction rates for halogenation of 2-methylthiazole at various temperatures

Temperature/K	Specific reaction rate (k_2)/$M^{-1}s^{-1}$		
	Iodination	**Chlorination**	**Bromination**
291.5	3.60	8.83	32.14
296.5	5.32	13.77	50.25
301.6	9.50	18.21	65.51
306.6	15.30	24.59	86.36
311.4	21.53	33.33	104.16

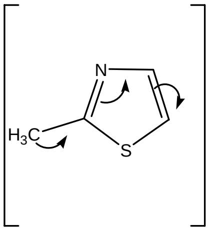
Several factors contribute to the rate of electrophilic substitution reactions. Electronegativity, size of the molecule, charge density, nature of the bond and the steric effect are some of the important factors. The above comparative study of the specific reaction rates of halogenation of 2-methylthiazole at a given temperature shows that the bromination is the fastest followed by chlorination while the iodination is the slowest. This can be explained on the basis of two important factors, that is elctronegativity of halogens and their charge density.

The elctronegativity of halogens are in order of Cl > Br > I, which shows that iodine is more positively charged. The elctrophiles are stronger, when they are more positive, thus according to the elctronegativity order of these halogens, iodine is said to be strong elctrophile. As stronger the elctrophile, more will be the rate of elctrophilic substitution reactions. It is thus expected that iodination should be faster among the halogenations.

In case of halogens, the order of size of these halogens are increasing down the group, i.e. I > Br > Cl. Since the charge density is the charge distribution over the volume of particle such as atom, it decreases with increase in atomic size. Thus, the charge density will decrease down the group as charge remains the same but size increases. The charge density of iodine is lower than that of bromine, and higher in chlorine. This decrease in charge density decreases the reactivity of the halogens while going down the group. This is due to fact that the decrease in charge density lessens the attraction for valence electrons of other atoms. Hence, the iodine is less reactive in elctrophilic substitution reaction even though it is more electropositive. Thus, iodine is more electropositive but has less charge density and chlorine is small in size having more charge density but less electropositive. In case of bromine both the factors are favorable than that for chlorine and iodine which makes bromine, better elctrophile. Thus, the bromination is observed to be the fastest followed by chlorination and iodination is the slowest.

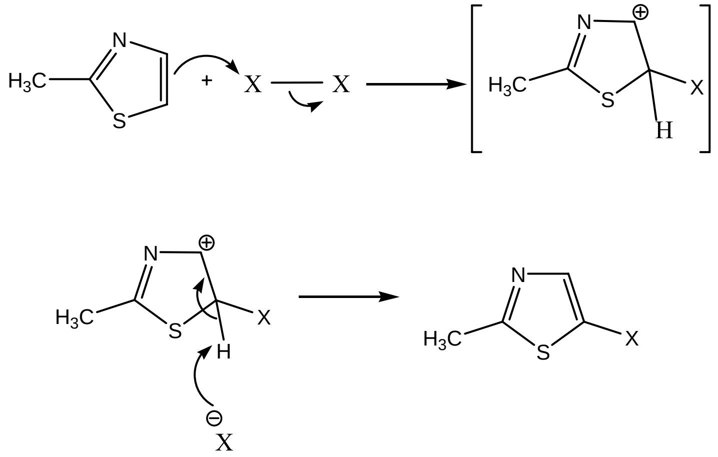
The mechanism of halogenations can be explained as follows.

The polarization of halogens (X_2) [where $X_2 = Br_2, Cl_2, I_2$] occurs in presence of polar solvent to create the bond dipole of the X-X bond. This dipole allows the halogen to have a formal positive charge on one halogen atom ($X^{\delta+}$) and formal negative charge on the other halogen atom ($X^{\delta-}$). The pi electron cloud of the double bond of the substrate i.e. 2-methylthiazole attacks the positive end or elctrophile $X^{\delta+}$, creating a resonance stabilized carbocation. Substrate loses the aromaticity in this step and becomes unstable. The negative end of the halogen $X^{\delta-}$ abstracts the proton and the molecule regains the stability by deprotonation of the carbocation. In the 2-methylthiazole, the electron donor methyl group always activates the position 5.



Also the halogens create electron density at C_5. Thus, 2-methylthiazole undergo halogenations at position 5 to yields the product as 2-methyl-5-halothiazole [18]. A plausible mechanism is shown below.

The kinetic measurements have been repeated at five different temperatures. The thermodynanamic parameters such as the energy of activation (E_a), enthalpy change of activation (ΔH^*) and entropy change of activation (ΔS^*) were evaluated[19].



Scheme I: Mechanism for halogenations of 2-methylthiazole

Table 3: Thermodynamic parameters for halogenation of 2-methylthiazole

S. No.	Parameter	For halogenation of 2-methylthiazole			Unit
		Iodination	**Chlorination**	**Bromination**	
1	Energy of activation (Ea)	64.80	48.50	38.39	kJ/mol
2	Pre-exponential factor (A)	1.59×10^{12}	4.58×10^{9}	2.92×10^{9}	$M^{-1}s^{-1}$
3	Enthalpy change of activation (ΔH*)	59.78	43.49	33.37	kJ/mol
4	Entropy change of activation (ΔS*)	-28.01	-76.63	-99.43	J/mol/k

It is clear from the thermodynamic data that in addition to the specific reaction rates, the energy of activation also indicates the order of halogenations. The activation energy is the highest for iodination while that for chlorination is higher than that for bromination of 2-methylthiazole. Bromination is thus observed to be faster than that of chlorination which is faster than that of iodination. The entropy of activation (ΔS*) for the reactions under study was calculated using energy of activation. The negative entropy of activation obtained in the present study indicates that the entropy decreases on the formation of the transition state, which often indicates the associate mechanism in which single activated complex is formed. The enthalpy of activation (ΔH*) has also been determined. It represents the difference in energy between the ground state and the transition state in a chemical reaction. The higher ΔH* is obtained for the iodination signifies that the more energy is required for the product formation. In general, a reaction is faster if ΔH* is small and the reaction rate is slower when ΔH* is large[20].

CONCLUSION

The relative reactivity of molecular halogens towards the halogenation has been qualitatively speculated hitherto. In the present study, quantitative assessment has been provided by the kinetic measurements of halogenation of 2-methylthiazole using molecular halogens X_2 ($X_2 = I_2, Cl_2, Br_2$). The reactions are observed to be rapid and follow second order kinetics. The hydrodynamic voltammetry technique was employed to follow the course of reactions. The specific reaction rates and thermodynamic parameters show that the bromination is faster followed by chlorination, which is faster than that of iodination. The study suggests that the relative reactivity of these three halogenating reagents is in order; $Br_2 > Cl_2 > I_2$ towards the halogenation of a given substrate in an electrophilic substitution reactions.

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