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Research Article

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Quantitative Assessment of Relative Reactivity of Pyrazole and Thiazole in Halogenation Reactions Using Hydrodynamic Voltammetry

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ABSTRACT

The kinetics of the halogenation of pyrazole and thiazole has been investigated using molecular chlorine and iodine. These are electrophilic substitution reactions and have been studied in aqueous medium. As the reactions are too rapid to be studied by conventional techniques, hydrodynamic voltammetry has been used to follow the progress of the reactions. The kinetic data for the two substrates and for the two different halogenating reagents provides relative substrate reactivity, which has been determined quantitatively. The thermodynamic parameters are calculated and correlated with the mechanism of the reactions.

Keywords: Kinetics; Rapid; Heterocycles; Chlorination; Iodination; Hydrodynamic voltammetry

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INTRODUCTION

Pyrazole and Thiazole are azoles which are a group of five membered heterocycles with two heteroatoms in the ring. These heterocycles comprise various pharmaceuticals having antitumor, anticancer, anti-HIV activities [1-5]. Heterocycles based efficient solar cells, organic semiconductors and electronics have also been receiving attention in recent years [6,7]. These compounds are highly reactive towards electrophilic attack. These substitution reactions seem important because of uses of these derivatives in synthetic and pharmaceutical intermediates [8-10]. Some of the halogenated derivatives are biologically active against various fungi and bacteria [11]. It therefore seems significant to study the kinetics of such halogenation reactions so that the quantitative assessment of relative reactivity can be determined. The kinetics of bromination of some five membered heterocycles such as imidazole, pyrazole and thiazole etc. have already been studied using brominating agents [12].
In view of the above, it is envisaged to study the kinetics of pyrazole and thiazole using two halogenating agents, molecular iodine and molecular chlorine. The reactions are too rapid to be studied by any conventional technique. Hence the present study is carried out by using a simple yet efficient technique, namely hydrodynamic voltammetry [13-15]. The data obtained by this study would be useful to assess the reactivity of two heterocycles with respect to two halogenating agents, which was lacking hitherto.

EXPERIMENTAL SECTION

Materials

Pyrazole and thiazole of analytical grade purchased from Sigma Aldrich were used in the present study and the required concentrations of the substrates were prepared in aqueous medium. Aqueous solution of molecular chlorine was prepared by using A. R. grade bleaching powder and concentrated hydrochloric acid. Dropwise addition of concentrated hydrochloric acid to 50 g bleaching powder liberates the Cl2 gas, which was collected in conductivity water with the following reaction -

$$CaOCl2+2HCl \rightarrow CaCl2+H2O+Cl2\uparrow$$

Molecular iodine solution was prepared using A. R. grade iodine crystals. Iodine crystals were dissolved by in conductivity water with occasional shaking and keeping overnight. Both the solutions viz. molecular chlorine and molecular iodine were stored in an air-tight and light-tight container. Prior to the study each time these solutions were standardized to determine their exact concentrations.

Method

Calibration of diffusion current

The electrodes used in the present study are rotating platinum electrode (RPE) [cathode] and saturated calomel electrode (SCE) [anode] connected in an electrical circuit of the cell. The halogenating agents undergo cathodic reduction by the following reactions:

$$Cl_2+2e^-=2Cl^-$$
$$I_2+2e^-=2I^-$$

Giving diffusion current in each case.

The diffusion current was measured in terms of galvanometer deflection using lamp and scale arrangement in cm which is converted into the unit of nano ampere (nA). The diffusion current values were recorded at various known concentrations of Cl_2 and I_2 in the required range. The calibration data for the various known concentrations of chlorine and iodine 298.35 K are shown in Table 1. Similarly calibration was carried out at five different temperatures prior to each kinetic measurement. Linear plots have been obtained for the diffusion current vs concentrations of Cl_2 and I_2.

Kinetic measurements: Equimolar solutions of Pyrazole and Chlorine both containing 100 fold potassium nitrate were poured simultaneously in a beaker assembled with RPE and SCE after attaining the desired temperature of the thermostat to make the total volume of 50.0 ml. At the moment of mixing a stopwatch was started. The extent of the reaction was measured by recording the diffusion currents at various time intervals. The use of large concentration of the supporting electrolyte i.e. KNO_3 ensures linear proportionality of the diffusion limited current at the RPE due to unreacted Cl_2.The diffusion current measured is a function of decaying concentration of Cl_2 at various time intervals. Reaction follows the second order kinetics and therefore half-life can be extended by diluting the solutions as per the following equation.

$$t_{1/2}=\frac{1}{a\,k}$$

where $t_{1/2}$ =half-life , a=initial concentration of the substrate and k=Specific reaction rate. This facilitates convenient kinetic measurements at various time intervals. As solutions are dilute, reaction times are small and the volume of the reaction mixture is small, green chemistry principles are followed. The concentrations of unreacted chlorine at these time intervals were determined from the calibration curve (Table 2).

The above procedure was repeated twice for checking the reproducibility of the galvanometer measurements and these were found to be within the limits of ±0.2 nA. The graph of $[Cl_2]^{-1}$ Vs time was found to be linear with the intercept equals to inverse of initial concentration of chlorine and the slope of the graph gives the value of the specific reaction rate. Similarly the kinetic measurements were repeated at five different temperatures. The results of are shown by Figure 1. The kinetic measurements were also repeated at five different temperatures for the iodination of pyrazole by molecular iodine. Similar studies have also been carried out for the kinetics of thiazole using Cl_2 and I_2 as halogenating agents.

Table 1: Calibration of the diffusion current due to molecular chlorine and molecular iodine at the temperature 298.3 K

[Cl2] (10-5M)	Galvanometer deflection (nA)	[I2] (10-4M)	Galvanometer deflection (nA)
0.2	9.1	0.8	9.3
0.4	17.9	1.6	17.4
0.6	24.2	2.4	24.7
0.8	33.4	3.2	33.0
1.0	40.0	4.0	40.0

Table 2: Kinetics of chlorination of pyrazole by molecular chlorine at 298.3 K

Initial concentration of Chlorine: 1×10^{-5}M; Initial concentration of Pyrazole : 1×10^{-5} M; Concentration of KNO_3: 1×10^{-3}M.

Time (s)	Diffusion current (nA)	[Cl2] (10-6M)	[Cl2]-1 (106 M-1)
10	31.1	7.4	0.135
20	17.9	6.7	0.149
30	26.0	6.1	0.163
40	22.8	5.4	0.185
50	21.0	4.9	0.204
60	18.1	4.1	0.243
70	16.5	3.8	0.263
80	15.8	3.7	0.270
90	15.1	3.5	0.285
100	14.8	3.2	0.312

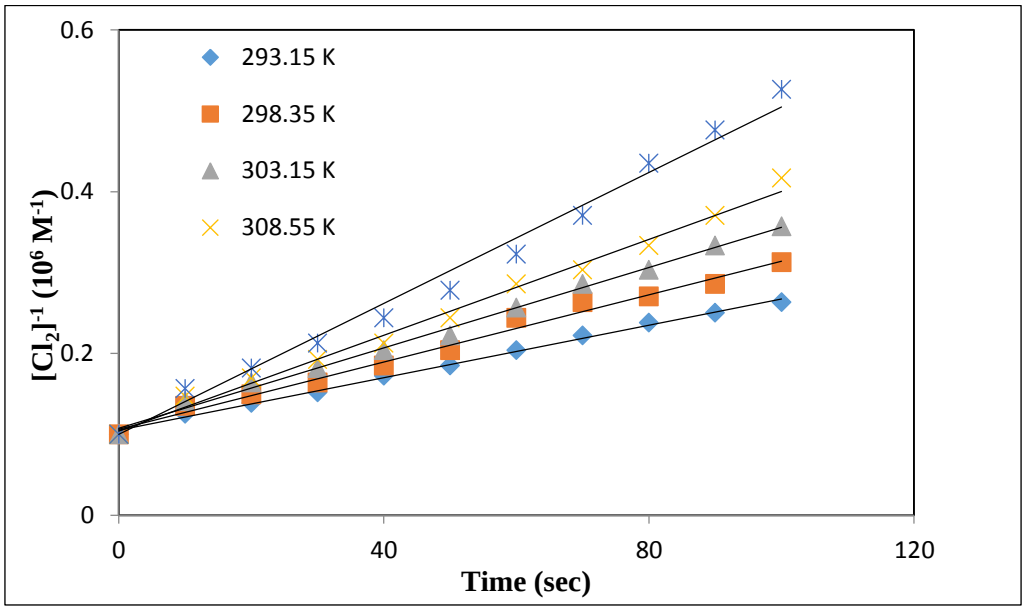

Figure 1: Kinetics of chlorination of pyrazole by molecular chlorine at different temperatures

RESULTS AND DISCUSSION

In the present study [Cl2] -1 or [I2] -1 versus time is a linear plot hence it is concluded that the reactions are of second order. The slope of the plots gives the specific reaction rates as per the second order equation,

$$k = \frac{1}{a\,t}\frac{x}{a-x}.$$

The kinetic measurements have an error of less than ±2% in view of the reproducibility of the diffusion current values.

The specific reaction rates (k) for the chlorination of pyrazole and thiazole at five different temperatures have been determined (Table 3). The study has also been repeated for the iodination of pyrazole and thiazole. The specific reaction rates for these iodination are given in Table 4.

The variation of specific reaction rate with the temperature helps to evaluate the thermodynamics parameters such as the energy of activation (Ea), enthalpy change of activation (Δ H*) and entropy change of activation (ΔS*) which are summarised in Tables 5 and 6.

Table 3: Variation of specific reaction rate with temperature for the chlorination of pyrazole and thiazole

Temperature (K)	Specific reaction rate constant (M-1 s-1)	
	Chlorination of Pyrazole	Chlorination of Thiazole
293.15	1697.8	1156.7
298.35	2169	1484.5
303.15	2591.1	1716.5
308.55	3022.3	2008.9
313.75	4046.2	2613.3

Table 4: Variation of specific reaction rate with temperature for the iodination of pyrazole and thiazole

Temperature (K)	Specific reaction rate constant k (M-1 s-1)	
	Iodination of Pyrazole	Iodination of Thiazole
293.15	9.43	8.24
298.35	15.22	11.60
303.15	23.09	13.80
308.55	28.54	15.11
313.75	41.84	20.13

Table 5: Kinetic and thermodynamic parameters for pyrazole

Parameters	Chlorination	Iodination
Specific Reaction Rate at 298.35 (M-1s-1)	2169	15.22
Energy of activation (kJmol-1)	27.57	39.51
Entropy of activation (Jk-1mol-1)	-105.26	-106.36
Enthalpy of activation (kJ mol-1)	26.61	34.55
Free energy of activation (kJ mole-1)	54.02	28.47

Table 6: Kinetic and thermodynamic parameters for thiazole

Parameters	Chlorination	Iodination
Specific Reaction Rate at 298.35 (M-1s-1)	1484.50	11.60
Energy of activation (kJmol-1)	31.47	48.25
Entropy of activation (Jk-1mol-1)	-95.33	-79.32
Enthalpy of activation (kJ mol-1)	26.57	43.29
Free energy of activation (kJ mole-1)	54.96	19.64

From the thermodynamic data and specific reaction rates, the energy of activation is determined and the order of halogenations is found. The activation energy (Ea) for chlorination of both the substrates is lower than that of iodination. Chlorination is thus faster than that of the iodination. The enthalpy of activation (ΔH^*) represent the difference in energy between the ground state and the transition state in a chemical reaction [16]. The higher ΔH^* obtained for the iodination of both the substrate than that of their chlorination signifies that the more energy is required for the product formation which makes the iodination reaction slower than that of chlorination. The negative entropy of activation (ΔS^*) obtained in the present study indicates that the entropy decreases on the formation of the transition state, which often indicates the associative mechanism with single activated complex formation.

Considering the kinetic and thermodynamic parameters the following relation is always true,
kchlorination>k iodination and kpyrazole >kthiazole
In all these cases the principle of stereochemistry has been quantitatively justified. Pyrazole is 1, 2 azole while thiazole is 1,3 azole. The two nitrogen atoms at 1, 2 positions in pyrazole are adjacent and they highly attract electron clouds towards them. This base weakening interaction of adjacent N atoms in pyrazole makes it less basic. In case of thiazole presence of sulphur reduces nucleophilicity of thiazole, therefore it is less reactive towards electrophilic substitution for the electronegative nitrogen withdraws electron density from the ring and makes it less reactive towards the electrophile.
The comparative study between iodination and chlorination of these substrates show that the specific reaction rates for the chlorination reactions are higher than that for iodination reactions.
Several factors contribute towards the electrophilic substitution reactions. Charge density is one of the important factors which explains the behaviour of halogenations. Even though iodine is more electropositive than chlorine it has less charge density than that of chlorine because of its greater size. The decrease in charge density reduces the attraction for valence electrons of neighbouring atom thereby decreasing the reactivity in electrophilic substitution reaction. Hence iodination seems to be slower than that of chlorination even though the iodine is more electropositive.
The mechanism of halogenation can be explained as follows.
The polarisation of halogens (X2) [where X2=Cl2 and I2] occurs in presence of polar solvent to create the bond dipole of the X-X bond.This dipole allows the halogens to have a formal positive charge on one halogen atom Xδ+and formal negative charge on the other halogen atom Xδ-. The pi electron cloud of the double bond of the substrates i.e. pyrazole and thiazole attacks the positive end or electrophile Xδ+, creating a resonance stabilised carbocation. Substrate loses the aromaticity in this step and becomes unstable. The negative end of the halogen Xδ- abstracts the proton and the molecule regains the stability by deprotonation of the carbocations.
The plausible mechanism is shown below which is iodination of pyrazole (Figure 2) and chlorination of pyrazole (Figure 3).

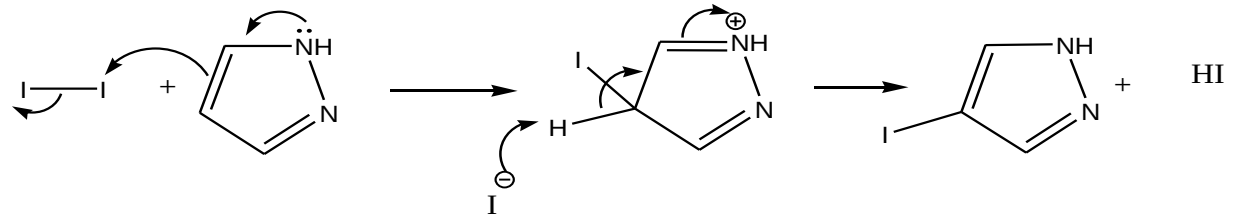

Figure 2: Iodination of pyrazole by I2 in aqueous medium

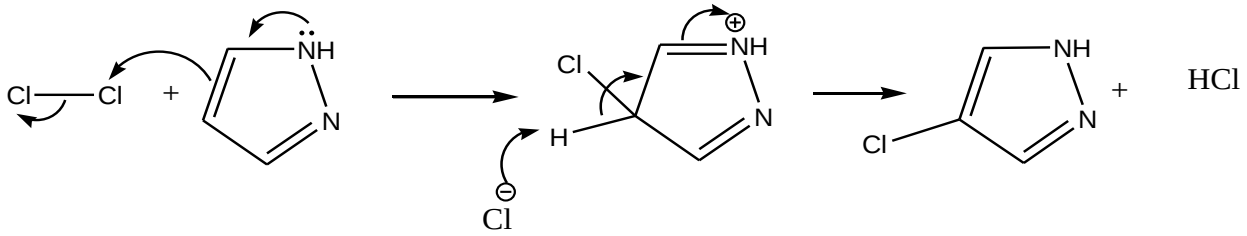

Figure 3: Chlorination of pyrazole by Cl2 in aqueous medium

Similar mechanisms can also be written for iodination of thiazoleby I2and chlorination of thiazole by Cl2 in an aqueous medium. Figure 4 shows the structure of 4-iodopyrazole and 4-chloropyrazole.
The products obtained in the present kinetic study were confirmed by recording the 1H NMR spectra. Figure 5 shows the 1H NMR spectrum for iodinated pyrazole. The appearance of doublet approximately at 7.1ppm (1H) at C3 and another doublet approximately at 7.5 ppm (1H) at C5 indicates the formation of mono iodo derivative. The broad singlet at 5.6ppm (1H) indicates the signal due to H attached to nitrogen at position 1. In Figure 6 1H NMR spectrum for the chlorinated pyrazole is shown. The appearance of doublet approximately at 7.1ppm (1H) at C3 and another doublet approximately at 7.5 ppm (1H) at C5 indicates the formation of mono chloro
derivative. The H attached to the nitrogen at position 1 gives the singlet at 9.9ppm. Both the spectrum confirms the substitution of iodine and chlorine takes place at position 4 in the pyrazole.

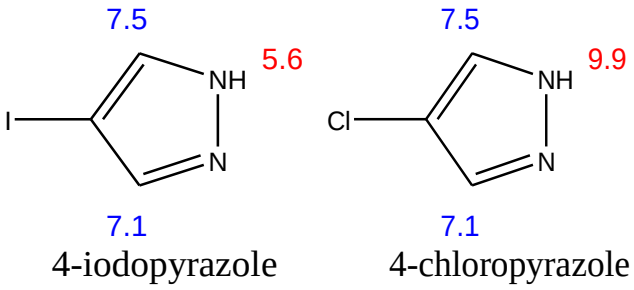

Figure 4: Structure of 4-iodopyrazole and 4-chloropyrazole

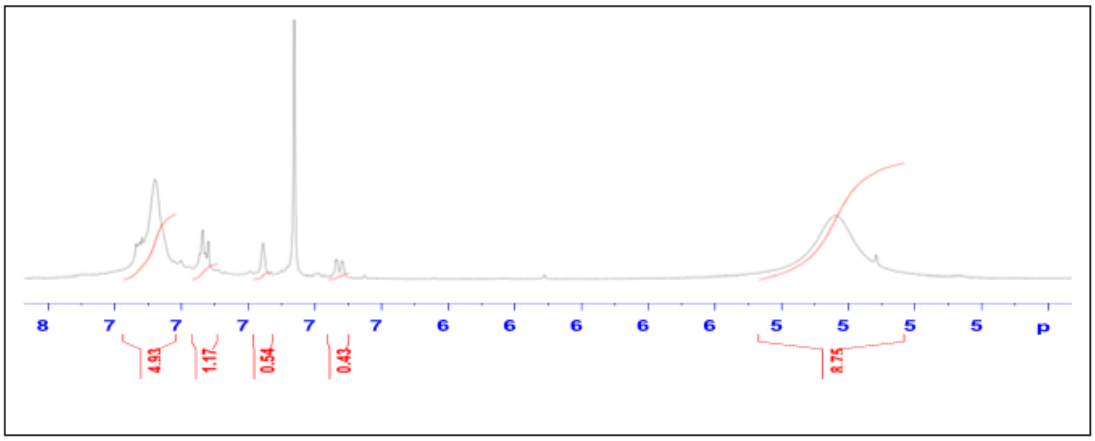

Figure 5: 1H NMR of 4-Iodopyrazole

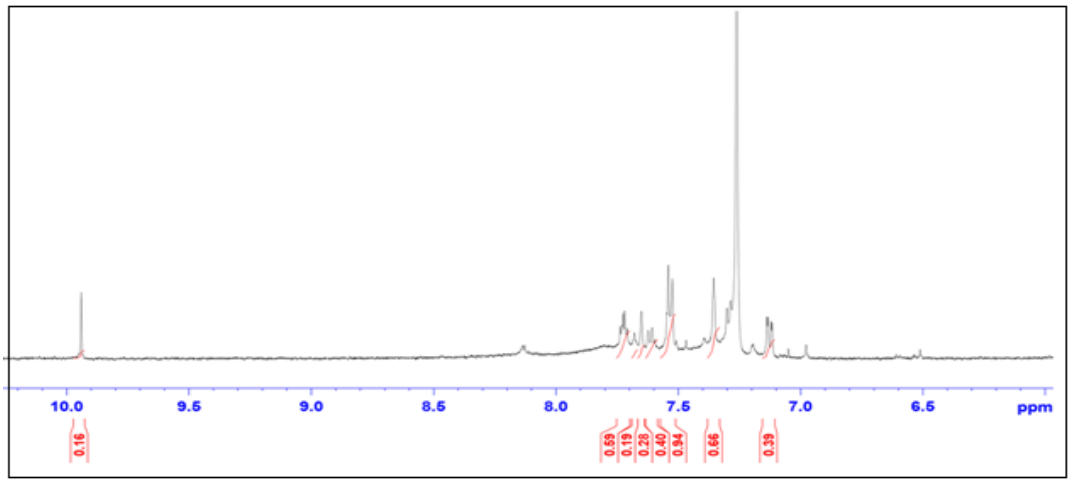

Figure 6: 1H NMR of 4-Chloropyrazole

Similarly the ^{1}H NMR of iodinated and chlorinated thiazole have also been recorded which confirms the mono halo derivative of thiazole.

CONCLUSION

The verification of the quantitative assessment of the relative reactivity of the two five membered aromatic heterocyclic compounds such as pyrazole and thiazole is provided by the kinetic studies of their chlorination and iodination in an aqueous medium. Even the thermodynamics parameters support the conclusion drawn above by the kinetic studies. The higher reactivity observed for the pyrazole than that of thiazole for both the halogenating

reagents is in accordance with the stereochemistry principles. The comparative reactivity of these two halogenating reagents thus has been provided quantitatively which was known qualitatively hitherto.

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REFERENCES

[1] V Kumar; V Sareen; V Khatri; S Sareen. Int J Appl Res. **2016**, 2(9), 461-469.
[2] MJ Alam; O Alam; P Alam; MJ Naim. Int J Pharm Sci Res. **2015**, 6(12), 1433-1442.
[3] MF Ahmad; SM Abdelrahman; MA Taha Eldebss; Abdel-Galil E Amr; AK Korany Ali; Naglaa A Abdel-Hafez; Mohamed M Abdulla. *Arch Pharm*. **2010**, 343(7), 384-396.
[4] WT Li; TR Hwang; CP Chen; CW Shen; CL Huang; TW Chen ; CH Lin ; Chang YL.; YY Chang; YK Lo ; HY Tseng ; CC Lin CC. *J Med Chem*. **2003**, 46, 1706.
[5] RV Patel ; P Kumari P; C Pannecouque ; E De Clercq ; KH Chikhaliafff . *Future Med Chem.* **2012**, 4(9), 1053-65.
[6] I Bulut; P Chavez; A Mirloup; Q Huaulme; A Hebraud; B Heinrich; S Fall; S Mery; R Ziessel; T Heiser; P Leveque; N Leclerc. *J Mater Chem C.* **2016**, 4, 4296-4303.
[7] Y Lin; H Fan; Y Li; X Zhan. *Adv Mater*. **2012**, 24, 3087-3106.
[8] MT Chhabria; S Patel; P Modi; PS Brahmkshatriya. *Curr Top Med Chem*. **2016**, 16(26) 2841-2862.
[9] G Li ; R Kakarla ; SW Gerritz. *Tetrahedron Lett*. **2007**, 48, 4595.
[10]AM Salaheldin; Oliveira Campos F; LM Rodrigues. *Tetrahedron Lett*. **2007**, 48, 8819- 8822.
[11]SB Walke; RP Bhadane; SB Deokar; SL Bonde. J Chem Pharm Sci. **2016**, 4(2), 61-69.
[12]SB Walke; SL Bonde; RP Bhadane ; VT Dangat ; B Jadhav. *Orient J Chem*. **2015**, 31(4), 2239-2245.
[13]Willayat Bashir; VT Borkar; VT Dangat. *Asian J Chem*. **2016**, 28(8), 1871-1872
[14]SL Bonde; VT Dangat; RP Bhadane; VS Joshi. *Int J Chem Kinet*. **2013**, 45(6), 355- 362.
[15]VT Borkar; SL Bonde; VT Dangat. *Int J Chem Kinet*. **2013**, 45, 693-702.
[16] JH Espenson. Chemical Kinetics and Reaction Mechanism, 2nd edition McGraw-Hill New York, **2002**, 156-160.