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Structure -Activity Correlation of Thiophene-2- Sulfonic Acid and Thiophene by Rapid Chlorination Kinetics using Hydrodynamic Voltammetry

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A B S T R A C T

The rapid chlorination kinetics of thiophene-2-sulfonic acid by molecular chlorine in aqueous solution has been investigated employing hydrodynamic volatammetry. The specific reaction rate and energy of activation for the reaction were found to be respectively 18 $M^{-1}s^{-1}$ and 53 kJ mol^{-1} at 24.5^0C. These data complemented with those for the chlorination of thiophene obtained under identical conditions, quantitatively ascertained the markedly less reactivity of thiophene-2-sulfonic acid relative to thiophene in these reactions. The substituent effect of the sulfonic acid moiety has been proposed as the cause of the difference in the reactivity of the two substrates.

Keywords: Chlorination, hydrodynamic voltammetry, thiophene-2-sulfonic acid

A R T I C L E I N F O

CONTENTS

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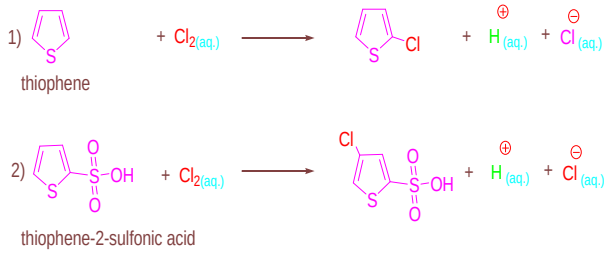
1. Introduction

The five member heterocycle thiophene is often used as an isosteric building block in drug design. [1] However, the thiophene moiety is considered a structure alert in molecular drug delivery due to the varying degree of idiosyncratic reactions associated with some drugs like clopidogrel containing such heterocycles. Consequently,

they have to be flagged for careful monitoring and restricted use because of toxicity. [2] The phamacokinetic profile of these drugs indicates that specific intermediates are responsible for the toxins formed. Hence structure-activity relationships (SARs) of thiophene derivatives need to be delved into. [3] Chlorination of drinking waters leads to the formation of trihalomethanes arising from the reactions of organic impurities with chlorine. Trace amount of chloroform is formed due to the presence of chlorination of phenols and trihydroxy benzenes present in water being chlorinated for disinfection.[4] Chlorinated 3,5-cyclo hexadienone and similar intermediates formed as precursors have been studied by the Membrane Introduction Mass Spectrometry (MIMS) technique. Formation of toxic by-products during the disinfection of drinking water by chlorination has invoked much interest in recent years in the field of green chemistry. [5] Marino has studied the halogenations of thiophene in acetic acid. Although numerous investigators have reported data on the gamut of halogenations of aromatic substrates in non-aqueous medium, the rarity of studies in purely aqueous medium is glaring. The reason for this lacuna is manifest from the difficulties encountered in following the kinetics of such reactions in aqueous medium which stem from their rapidity. In purely aqueous medium, the halogenations of aromatic substrates, especially brominations and chlorinations are very rapid necessitating special techniques to follow their kinetics instead of conventional methods. The half-lives of these reactions are often a few seconds only and setting up innovative techniques to follow the course of such reactions is a challenging task.[6,7] Among the halogenations of aromatic substrates, brominations are the fastest and iodinations slowest, albeit catalysts and pH of the reaction medium significantly affect the reaction rates. Numerous chlorinating reagents such as acidified solutions of hypohalous acid, chloramine T, N-chloro succinamide and molecular chlorine are used to carry out these reactions in different medium. The need for a detailed insight into the mechanisms of chlorination reactions of aromatic substrates especially thiophene and its derivatives in aqueous medium through kinetics and other studies thus seems justified. In the present study, the chlorination of thiophene sulfonic acid by molecular chlorine in aqueous solution at 7 pH was carried out at various temperatures. [8] The reaction was found to be rapid and a special technique - hydrodynamic voltammetry was necessitated for kinetic investigations to monitor the fall in the concentration of chlorine with the progress of the reaction.[9] Reaction 2 was presently studied while Reaction 1 has been reported earlier.



The product of Reaction 2 is 4-chorothiophene-2-sulfonic acid. The formation of the mono-chloro isomer in the reaction was ascertained stoichiometrically and confirmed from NMR data. Among the reactants and products in the reaction, chlorine being the only electro-reducible species, its concentration as the reaction proceeds was followed in terms of diffusion current at a micro-cathode. The reference electrode was a saturated calomel electrode.

2. Materials and Methods

Chemicals:

AR grade thiophene-2-sulfonic acid, sodium dihydrogen phosphate, disodium hydrogen phosphate and potassium nitrate were used to prepare the required stock solutions in double distilled water. Chlorine was prepared from bleaching powder and concentrated hydrochloric acid. It was bubbled through water to free it from HCl and the strength was determined from iodometric titration.

Electrodes:

The cathode was a platinum micro-electrode (RPE) fused to a glass tube rotated at 600 rpm with aid of a motor. The anode was a saturated calomel electrode (SCE).

Calibration of diffusion current:

The RPE & SCE were dipped in 50.0 cm^3 of 0.10 M potassium nitrate which was the supporting electrolyte and contained the required buffer solutions. A potential of + 0.2 V versus the SCE was applied at the RPE by means of potentiometric arrangement. The galvanometer light spot showed zero deflection on the scale. Potassium nitrate solution was then replaced by 50.0 $cm^3$of 0.001M chlorine solution containing 0.10 M potassium nitrate and the required amount of the buffer component to maintain 7 pH. The shunt was adjusted for the deflection of the galvanometer light spot to be a maximum but within scale limit. Keeping this shunt value constant for all the temperatures and during the kinetic readings, the diffusion current in terms of deflection of the galvanometer light spot was recorded for various concentrations of chlorine in the range between 1.0 x 10^{-3} and 0.2 x 10^{-3} M. The plots of diffusion current versus concentration of chlorine for various temperatures were found to be linear as shown in Table 1 and Figure 1. Calibration was carried out only after the solutions had attained the thermostat temperatures at which the kinetic readings were subsequently observed.

Kinetic measurements:

Additions of the reactants were made in the following manner. 25 cm^3 of 2 x 10^{-3} M each of thiophene-2-sulfonic acid and chlorine containing 0.01 M potassium nitrate and the required buffer components were kept in separate flasks in a thermostat. After the thermostat temperature was attained by the solutions, the two reactants were simultaneously added to the reaction vessel kept in the thermostat in which the RPE was rotating and SCE was dipped. The time at the moment of mixing was noted and the diffusion current due to the un-reacted chlorine was recorded at every ten seconds in terms of the galvanometer light spot for a minute.From the calibration plot at the relevant temperature, the un-reacted concentration of chlorine at various instants of time was evaluated for the kinetic run. The above procedure of calibration and kinetic

measurements was repeated thrice to check the reproducibility of the galvanometer measurements, which were found to be within + 0.2 nA i.e. ± 0.2 cm error.

Determination of the energy of activation:

These studies were carried out at various temperatures in the range 10-25^{0}C from which the thermodynamic parameter- energy of activation E_a, was evaluated.

Table 1: Calibration of the diffusion current of chlorine at various temperatures

$[Cl_2]$ / 10^{-3}M	Mean diffusion current / nA				
	10.2^{0}C	12.2^{0}C	16.3^{0}C	20.2^{0}C	24.5 ^{0}C
0.2	6.1	6.5	7.0	7.6	8.2
0.4	12.1	13.0	14.1	15.1	16.1
0.6	18.2	19.4	20.9	22.8	24.3
0.8	24.0	26.1	28.0	30.4	32.5
1.0	30.5	32.4	35.0	38.1	41.2

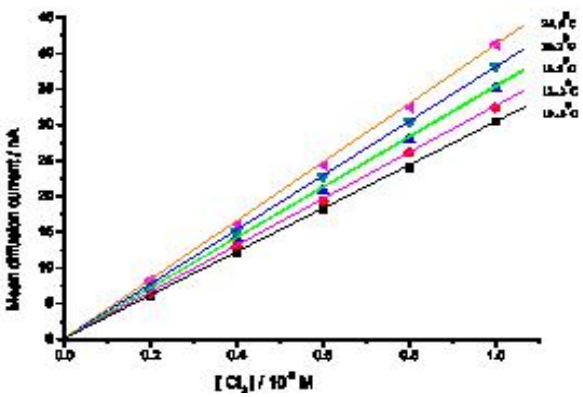


Figure 1: Calibration of diffusion current

Table 2: Parameters in the kinetics of chlorination of thiophene-2-sulfonic acid

S.No	Parameter	Value	Unit
1	Potential applied at the RPE Vs SCE	0.2	V
2	Initial concentration of chlorine	1 x 10^{-3}	M
3	Initial concentration of thiophene	1 x 10^{-3}	M
4	Concentration of potassium nitrate	1 x 10^{-1}	M
5	Concentration of NaH_2PO_4	2.385	m mol
6	Concentration of Na_2HPO_4	2.615	m mol
7	Total volume of the reaction mixture	50.0	cm^3

3. Results and Discussion

The plot of $[Cl_2]^{-1}$ Vs time was linear and hence the reaction under study was concluded to be of the second order. The slope this plot is the specific reaction rate of the reaction. The slope of the Arrhenius plot is used to calculate the energy of activation for the reaction. The kinetic and related thermodynamic data for the chlorination of thiophene-2-sulphonic acid were complemented with those for thiophene under identical conditions. This conclusively indicated the relative reactivity of the two substrates, thiophene and thiophene-2-sulphonic acid in the chlorination reactions in quantitative terms (Table 4). The rotating micro-cathode detected very low concentrations of un-reacted chlorine which is the only electro-reducible species among the reactants and products in the reaction under study. The diffusion current measured under these conditions of a hundredfold concentration of the supporting electrolyte was proportional to the chlorine concentration. The phosphate buffer system, Na_2HPO_4 and NaH_2PO_4 was used to maintain 7.0 pH.

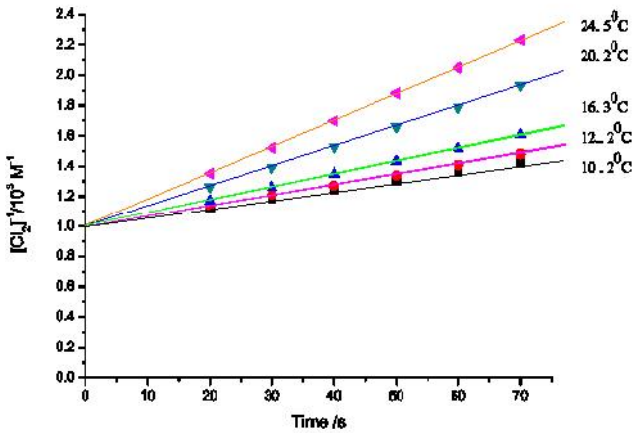


Figure 2: Kinetics of chlorination of thiophene-2-sulfonic acid at various temperatures

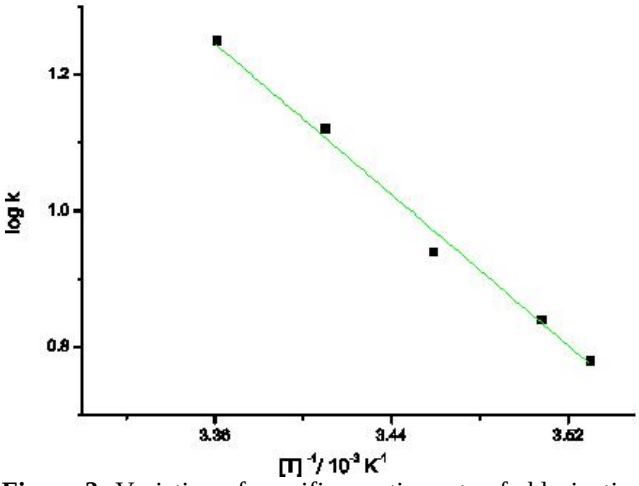


Figure 3: Variation of specific reaction rate of chlorination of thiophene-2-sulfonic acid with temperature : Arrhenius plot

The fourfold greater reactivity of thiophene relative to that of thiophene-2-sulfonic acid may be explained as follows. The pi electron cloud of the double bond adjacent to the S atom in the thiophene molecule attacks the positive end of the Cl_2 molecule. Subsequently the thiophene-2-sulfonic acid molecule loses its aromaticity and becomes unstable.

The –ve end of the Cl_2 molecule abstracts the proton in the fast step to stabilize the molecule to re-attribute aromaticity to it with the release of H^+ and Cl^- ions. The five member ring of thiophene is less aromatic than the six member rings of benzene derivatives like aniline and hence only a mono-chloro product is formed. Chlorine is known to hydrolyze in aqueous solution according to the equilibrium

$$Cl_2 + H_2O \rightleftharpoons HOCl + H^+ + Cl^-$$

The forward and reverse specific rates of this hydrolysis equilibrium are $1.1\times10^1\ s^{-1}$ and $2.6\times10^4\ M^{-2}\ s^{-1}$ respectively. Aromatic substrates are known to react very slowly with hypohalous acids as compared to molecular halogens. Hence all the equilibrium concentration of HOCl is rapidly converted into the more reactive species – the chlorine molecule, which may be considered to be the sole chlorinating species. The possibility of protonated H_2OCl^+ as the prime chlorinating species or a catalytic effect of H^+ on the halogenation is ruled out as the pH of the reaction is 7. [10]

Table 3: Kinetics of chlorination of thiophene-2-sulfonic acid by chlorine at 24.5^0 C

Time /s	Diffusion current/ nA				$[Cl_2]/10^{-3}$ M	$[Cl_2]^{-1}/10^3\ M^{-1}$
	1	2	3	Mean		
20	30.8	30.6	31.0	30.8	0.74	1.35
30	27.0	27.0	27.0	27.0	0.66	1.52
40	24.0	24.1	14.0	24.0	0.59	1.70
50	21.7	21.6	21.8	21.7	0.53	1.88
60	20.0	20.0	20.0	20.0	0.49	2.05
70	18.5	18.6	18.4	18.5	0.45	2.23

Table 4: Comparison of the kinetic and thermodynamic parameters for the chlorination of thiophene and thiophene-2-sulfonic acid in aqueous solution at 25.0^0C

S.No	Parameter	Thiophene	Thiophene-2-sulfonic acid
1	Initial reactant concentration / M	5×10^{-4}	1×10^{-3}
2	Specific reaction rate / $M^{-1}s^{-1}$	83	18
3	Half-life /s	24	56
4	Energy of activation / kJ mol^{-1}	41.6	53.0

4. Conclusion

The reduced reactivity for chlorination of thiophene-2-sulfonic acid relative to thiophene is quantitatively established in this kinetic investigation. The lower reactivity is manifest from the higher energy of activation stemming from the relatively lower specific reaction rate for the chlorination of the less nucleophilic thiophene sulfonic acid compared to the thiophene. Thus, the assertion of the speculated reactivities of the two aromatic substrates, thiophene and thiophene-2-sulfonic acid for the uncatalyzed chlorination at 7 pH in aqueous medium is herein justified on a quantitative basis.

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