

A Quantitative Assessment of the Relative Reactivities of the Regioisomers of Resorcylic Acid by Hydrodynamic Voltammetry

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ABSTRACT

The rapid chlorination kinetics of the regioisomers of resorcylic acid in aqueous medium by molecular chlorine at 7 pH has been studied by hydrodynamic voltammetry. The specific reaction rates for the chlorination of the alpha, beta and gamma isomers have been found to be 333, 867 and 170 $M^{-1}s^{-1}$ at 27.0^o C respectively, thereby providing a quantitative estimation of the relative reactivities of these isomers elucidating the steric compulsions in the dynamics of these reactions.

Key Words : Chlorination, Resorcylic Acid, Hydrodynamic Voltammetry

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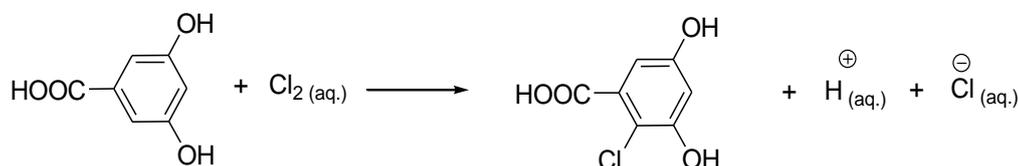
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I. INTRODUCTION

Halogenations of aromatic substrates in aqueous solution invariably yield products that are precursors of drug molecules. These have pharmacodynamic significance as anti-tumor, anti-viral, and anti-bacterial compounds [Shunji et al, 2010]. Besides, they are of importance in organic synthesis in coupling reactions [Suzuki, 1999]. The reactivity of these substrates are a result of their nature, the moieties present on them, substituent regioselectivity, steric compulsions of the reaction dynamics, reagent used, and solvent. The relative reactivity of different regioisomers in these reactions have often been qualitatively speculated but a quantitative assessment has been found lacking presumably due to the rapidity of these reactions in aqueous medium necessitating special techniques for their study. Herein we have adopted the hydrodynamic voltammetry technique to quantitatively assess the reactivity of the three regioisomers of resorcylic acid in aqueous medium in the chlorination reactions [Borkar et al, 2013]. The results have been invoked to quantitatively justify the relative ease of the mechanistic route in these reactions and thereby estimate the reactivity of the regioisomers as evidenced from these investigations.

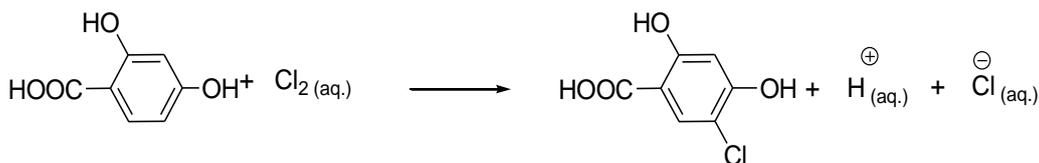
The three reactions under study are as follows;

a) Chlorination of alpha resorcylic acid (3,5-dihydroxy benzoic acid) by Cl_2



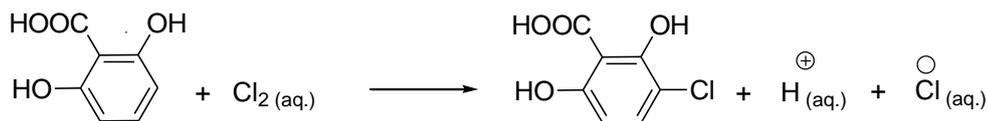
3,5-DIHYDROXY BENZOIC ACID

b) Chlorination of beta resorcylic acid (2,4-dihydroxy benzoic acid) by Cl_2



2,4-DIHYDROXY BENZOIC ACID

c) Chlorination of gamma resorcylic acid (2,6-dihydroxy benzoic acid) by Cl_2



2,6-DIHYDROXY BENZOIC ACID

In these reactions, chlorine is the lone species among the reactants and products that is electroreducible. The reaction can be followed by measuring the decaying diffusion current due to chlorine in the reaction, at a microcathode.

II. MATERIALS AND METHOD

Preparation of solutions

Stock solutions of the supporting electrolyte potassium nitrate and the three regioisomers of resorcylic acid are prepared in conductivity water using AR grade chemicals. Chlorine water is prepared from bleaching powder, freed from HCl and standardized iodometrically.

Electrodes

The positive electrode is a platinum microcathode (RPE) rotating at 600 rpm
The negative electrode is the saturated calomel electrode (SCE)

Calibration of the diffusion current

Diffusion currents at the RPE for different concentrations of chlorine solutions containing a hundredfold concentration of the supporting electrolyte are determined. [Table 1]. The plots of diffusion current Vs concentration are found to be linear at all temperatures.

Kinetic readings

Equal concentrations of resorcylic acid and chlorine containing the supporting electrolyte and the buffer solutions to maintain 7 pH, are mixed along in a reaction vessel kept in a thermostat. The two electrodes are contained in this reaction vessel and the time is noted. At every 10 seconds, the decreasing diffusion current values are recorded for at least one half-life of the reaction.

The plots of $[\text{Cl}_2]^{-1}$ Vs time are found to be linear at all temperatures. The slopes of these plots are the specific reaction rates of the reactions under investigation. Table 2 shows a typical set of data for the chlorination of beta resorcylic acid by molecular chlorine in aqueous solution at 25.0°C and 7 pH.

Table 1: Calibration of diffusion current for molecular Chlorine at various temperatures
Potential applied at the RPE Vs SCE: 0.1 V

| [Cl ₂] / 10 ⁻⁵ M | Mean diffusion current / nA | | | | | | |
|--|-----------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | 10.0 ⁰ C | 15.0 ⁰ C | 20.0 ⁰ C | 25.0 ⁰ C | 30.8 ⁰ C | 35.9 ⁰ C | 40.5 ⁰ C |
| 0.5 | 3.8 | 4.2 | 4.6 | 5.0 | 5.5 | 5.7 | 6.3 |
| 1.0 | 7.8 | 8.6 | 9.3 | 10.1 | 10.8 | 11.6 | 12.2 |
| 2.0 | 15.7 | 17.0 | 18.5 | 20.0 | 21.5 | 23.0 | 24.2 |
| 3.0 | 23.4 | 25.8 | 27.9 | 30.1 | 32.4 | 33.8 | 36.0 |
| 4.0 | 31.4 | 34.2 | 37.1 | 40.1 | 43.0 | 46.0 | 48.5 |

Table 2: Kinetics of chlorination of beta Resorcylic Acid at 25.0°C by molecular chlorine

| time /s | diffusion current / nA | | | | [Cl ₂] / 10 ⁻⁵ M | [Cl ₂] ⁻¹ /10 ⁴ M ⁻¹ |
|---------|------------------------|------|------|------|--|--|
| | 1 | 2 | 3 | Mean | | |
| 20 | 23.3 | 23.5 | 23.0 | 23.2 | 2.33 | 4.30 |
| 30 | 19.2 | 19.0 | 19.4 | 19.1 | 1.92 | 5.20 |
| 40 | 16.4 | 16.4 | 16.6 | 16.4 | 1.65 | 6.10 |
| 50 | 14.3 | 14.3 | 14.2 | 14.3 | 1.43 | 7.00 |
| 60 | 12.7 | 12.7 | 12.7 | 12.7 | 1.27 | 7.90 |

Slope of plot of $[\text{Cl}_2]^{-1}$ Vs time = specific reaction rate k for the chlorination of beta resorcylic acid in aqueous solution at 25.0°C and 7 pH = 867 M⁻¹s⁻¹

III. RESULTS AND DISCUSSION

The chlorination reactions of all the three regioisomers are found to be rapid and follow second order kinetics as the plots of $[\text{Cl}_2]^{-1}$ Vs time are linear. The formation of the monochloro derivatives in all the three cases is ascertained by stoichiometry and by NMR investigations. The results are presented in Table 3.

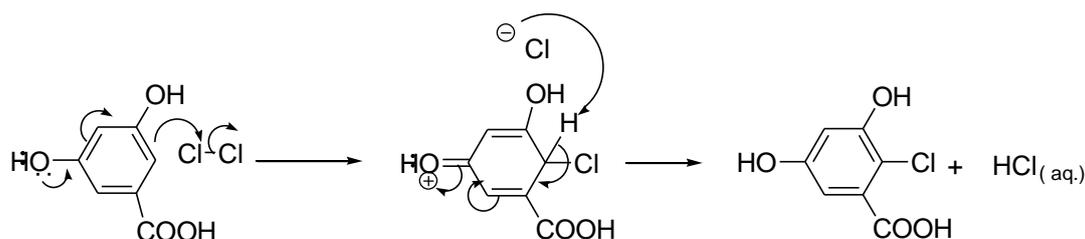
Table 3: Specific reaction rates k , at 25.0°C for the chlorination of resorcylic acid isomers

| Sr.No. | Regioisomer of resorcylic acid | $k/\text{M}^{-1}\text{s}^{-1}$ |
|--------|--------------------------------|--------------------------------|
| 1 | Alpha | 333 |
| 2 | Beta | 867 |
| 3 | Gamma | 170 |

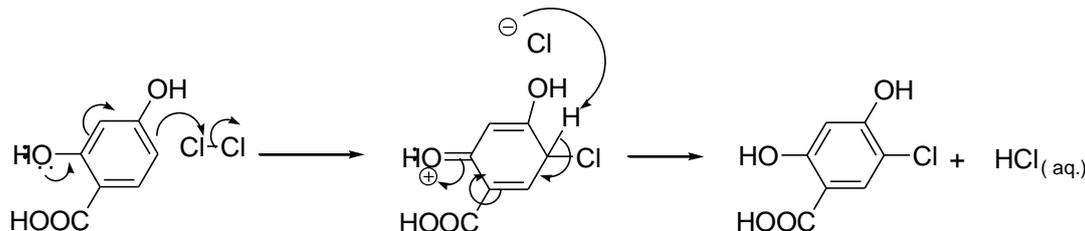
Molecular chlorine is the sole chlorinating agent in the reactions in view of the equilibrium
 $\text{Cl}_2 + \text{H}_2\text{O} = \text{HOCl} + \text{HCl}$ [$k_{\text{equil}} = 3.94 \times 10^{-4}$ at 25.0°C] [Deborde and Gunten 2008]

The probable mechanism for the chlorination of the three isomers may be suggested as follows;

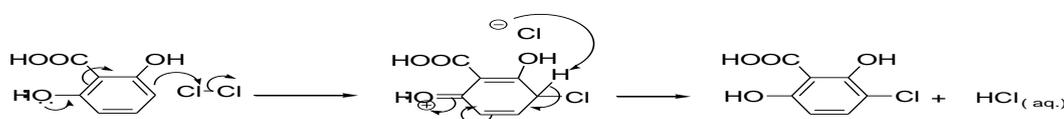
a) Chlorination of alpha resorcylic acid (3,5-dihydroxy benzoic acid) by Cl_2



b) Chlorination of beta resorcylic acid (2,4-dihydroxy benzoic acid) by Cl_2



c) Chlorination of gamma resorcylic acid (2,6-dihydroxy benzoic acid) by Cl_2



IV. CONCLUSION

The values of the specific reaction rates for the chlorination of the resorcylic acid regioisomers in aqueous medium at 27.0°C presented in Table 1 obtained in this study, may be interpreted as follows. The $-\text{COOH}$ group being electron withdrawing, is meta directing while the $-\text{OH}$ group is electron donating, hence is ortho and para directing. In beta resorcylic acid, the two $-\text{OH}$ groups and the $-\text{COOH}$ group activate position 5 in unison, relative to position 3 due to steric congestion at the latter. Hence 5-chloro-1,3-dihydroxy benzoic acid is formed at the fastest rate among the three regioisomers studied. Gamma resorcylic acid evinces the slowest relative rate as there is crowding of the bulky $-\text{COOH}$ group with the two $-\text{OH}$ groups. The proximity of these substituents is conducive to intramolecular hydrogen bonding among them resulting in attenuated nucleophilicity of the benzene ring. This is reflected in the slowest rate observed. In alpha resorcylic acid, the two $-\text{OH}$ groups block the positions meta to the $-\text{COOH}$ group resulting in the formation of the 2-chloro-3,5-dihydroxy benzoic acid. The position between the two $-\text{OH}$ groups is less activated due to steric hindrance.

These steric compulsions are reflected in the relative reactivity of the regioisomers under study in a quantitative manner in these investigations.

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