The Rapid Iodination of Salicylic Acid in Aqueous Medium by Iodine Monochloride using Hydrodynamic Voltammetry

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Abstract
The rapid kinetics of iodination of salicylic acid by iodine monochloride at 7 pH has been studied at five different temperatures. The reaction is very fast and of the second order, having half-life 300 seconds and rate constant 6.81 M⁻¹s⁻¹ at 30.2°C. The reaction is fast and hydrodynamic voltammetry, a special technique to follow the rapid iodination kinetics is employed. The energy of activation, entropy change in the reaction and the frequency factor in the reaction are evaluated. The kinetic and related thermodynamic data obtained are used to comment on the reactivity of the substrate.

Keywords: Iodine monochloride, hydrodynamic voltammetry, salicylic acid, fast reaction.

Introduction
Iodine monochloride is an interhalogen compound with the formula ICl. The molecular mass of iodine monochloride is 162.35 g/mol and density is 3.10 g/cm³. It is soluble in CS₂, acetic acid, pyridine, alcohol, ether and water.

ICl is polar and is a potential source of I⁻. Iodinations of aromatic substrates in aqueous medium yield iodo derivatives that have significance in pharmacodynamics, as moieties of drugs having antiseptic, disinfectant, antiviral and anti-bacterial properties.

The rapidity of halogenations of aromatic substrates in aqueous medium necessitates the use of special techniques to measure the reaction rates. These include temperature jump, stopped flow and pulse radiolysis techniques.

We have herein adopted a relatively simple yet efficient technique, Hydrodynamic Voltammetry, to monitor the rate of the fast iodination of salicylic acid by iodine monochloride in aqueous solution.

Iodine monochloride being the lone species in the reaction that is electroactive at a microelectrode its decay as the reaction proceeds is monitored by determining the nanocurrent at a platinum microelectrode that rotates at 1000 rpm. The following are the half-cell reactions at the two electrodes in the galvanic cell used in this hydrodynamic voltammetry technique.

ICl + 2e⁻ → I⁻ + Cl⁻ At the positive electrode, RPE
2Hg + 2Cl⁻ → Hg₂Cl₂ + 2e⁻ At the negative electrode, SCE
ICl+ 2Hg + 2Cl⁻ → Hg₂Cl₂ + I⁻ + Cl⁻ Overall reaction

The use of hundredfold molar KNO₃ ensures linear proportionality of the nanocurrent at the RPE generated by iodine monochloride.

Preparation of Solutions: Iodine Monochloride: A stock solution of iodine monochloride is prepared in double distilled water. The strength of this solution is determined iodometrically.

Salicylic Acid: The required weight of A.R. grade of salicylic acid is used to prepare the stock solutions in water.

Buffer Solutions: Na₂HPO₄ and NaH₂PO₄ each of 0.4 molarity are prepared as buffer solutions.

Potassium Nitrate: A.R. grade potassium nitrate is used to prepare a stock solution of which is used as the supporting electrolyte.

Scheme-1
The reaction between Salicylic acid and ICl
Material and Methods

Construction of the RPE: The rotating platinum electrode (RPE) consists of a 0.5 mm diameter platinum wire fused to one end of inverted 'T' shaped glass tube having 6 mm diameter, such that a centimeter of the platinum wire protrudes out. A pulley and a pair of ball-bearing are mounted on this glass tube, having the total length of 32 cm. The ball bearings are fixed to a stand. A pulley is connected to a synchronous motor. The radius of the pulley is so adjusted that the electrode rotates at a speed of 600 rpm. Some mercury kept inside the glass tube and a silver wire is inserted for electrical contact. The lower 4 cm portion of the glass tube effects a stirring action in the solution when the electrode is rotated. A constant potential of +0.1 V versus the saturated calomel electrode (SCE) is applied at the RPE, using a potentiometer.

A galvanometer with the sensitivity of 0.10 nA cm⁻¹ provided with a lamp and scale arrangement is employed to register the nanocurrent due to iodine monochloride. The current passing through the galvanometer is controlled by employing a shunt.

Calibration of Readings: The two electrodes are dipped in 50.0 cm³ of 5x10⁻³ M KNO₃ which is the supporting electrolyte. +0.1 V versus the reference electrode is applied at the rotating platinum cathode. The galvanometer light spot is adjusted to zero deflection on the scale. KNO₃ solution is then replaced by 5x10⁻⁴ M iodine monochloride solution containing 5x10⁻² M potassium nitrate. The nanocurrent due to iodine monochloride in the range 1x10⁻³ M to 5x10⁻⁴ M is recorded. A typical calibration plot is depicted in figure 1.

The procedure is repeated at five different temperatures using a thermostat.

Kinetic Measurements: 25 cm³ of 1x10⁻⁴ M salicylic acid containing 0.1 M KNO₃ and 1x10⁻⁴ M iodine monochloride containing 25 cm³ of 0.1 M potassium nitrate containing Na₃H₂PO₄ and NaH₂PO₄ are maintained in a thermostat in separate flasks. While mixing the contents of the two flasks in the reaction vessel containing the electrodes, a stop-clock is started and the attenuating nanocurrent due to ICl is monitored.

The above procedure of calibration and kinetic measurement is repeated for checking the reproducibility of the galvanometer measurements, and these are found to be within the limits of 0.2 cm.

Results and Discussion

From the deflections noted during the kinetic study, the unconsumed iodine monochloride, is determined using figure 1. A plot of [ICl]⁻¹ i.e. 1/(a-x) versus 't' is a straight line ascertaining the order of the reaction to be two.

The gradient of this plot gives the specific reaction rate 'k'.
Figure 2: Plot of reciprocal of concentration of unconsumed ICl versus time.

Figure 3: Arrhenius Plot for the iodination of salicylic acid by ICl.
These studies are repeated in the temperature range 10-30°C, from which the energy of activation, \( E_a \) for the reaction is evaluated. Further, the frequency factor, \( A \) and the entropy change \( \Delta S \) are also calculated.

**Table-1**

Calibration of the diffusion current of iodine monochloride at various temperatures for iodination of salicylic acid (± 0.2 nA error)

<table>
<thead>
<tr>
<th>ICl/10^-3 M</th>
<th>10.1°C</th>
<th>15.4°C</th>
<th>20.1°C</th>
<th>25.2°C</th>
<th>30.2°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.1</td>
<td>2.4</td>
<td>2.8</td>
<td>3.3</td>
<td>3.6</td>
</tr>
<tr>
<td>2</td>
<td>4.2</td>
<td>4.8</td>
<td>5.7</td>
<td>6.5</td>
<td>7.2</td>
</tr>
<tr>
<td>3</td>
<td>6.4</td>
<td>7.2</td>
<td>8.4</td>
<td>9.8</td>
<td>10.8</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
<td>9.8</td>
<td>11.2</td>
<td>13.2</td>
<td>14.4</td>
</tr>
<tr>
<td>5</td>
<td>10.4</td>
<td>12.1</td>
<td>14.2</td>
<td>16.2</td>
<td>18.0</td>
</tr>
</tbody>
</table>

**Table-2**

Kinetics of iodination of salicylic acid by using iodine monochloride at 10.1°C (±0.2 nA error)

<table>
<thead>
<tr>
<th>Time/s</th>
<th>Diffusion Current/nA</th>
<th>[ICl]/10^-4 M</th>
<th>[ICl]²/10^7 M^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.4</td>
<td>5.0</td>
<td>2.0</td>
</tr>
<tr>
<td>50</td>
<td>10.0</td>
<td>4.8</td>
<td>2.1</td>
</tr>
<tr>
<td>100</td>
<td>9.3</td>
<td>4.5</td>
<td>2.2</td>
</tr>
<tr>
<td>150</td>
<td>8.9</td>
<td>4.3</td>
<td>2.5</td>
</tr>
<tr>
<td>200</td>
<td>8.7</td>
<td>4.2</td>
<td>2.4</td>
</tr>
<tr>
<td>250</td>
<td>8.3</td>
<td>4.0</td>
<td>2.5</td>
</tr>
<tr>
<td>300</td>
<td>7.7</td>
<td>3.7</td>
<td>2.7</td>
</tr>
<tr>
<td>350</td>
<td>7.5</td>
<td>3.6</td>
<td>2.8</td>
</tr>
<tr>
<td>400</td>
<td>7.0</td>
<td>3.4</td>
<td>2.9</td>
</tr>
</tbody>
</table>

**Table-3**

Variation of rate constant of iodination of salicylic acid by iodine (±0.2 error)

<table>
<thead>
<tr>
<th>Temp/K</th>
<th>[T]^2/10^-2 K^-1</th>
<th>k/M^1s^-1</th>
<th>log k</th>
</tr>
</thead>
<tbody>
<tr>
<td>283.1</td>
<td>3.53</td>
<td>1.70</td>
<td>0.2304</td>
</tr>
<tr>
<td>288.4</td>
<td>3.46</td>
<td>2.50</td>
<td>0.3979</td>
</tr>
<tr>
<td>293.1</td>
<td>3.41</td>
<td>3.41</td>
<td>0.5321</td>
</tr>
<tr>
<td>298.2</td>
<td>3.35</td>
<td>5.10</td>
<td>0.7075</td>
</tr>
<tr>
<td>303.2</td>
<td>3.29</td>
<td>6.81</td>
<td>0.8331</td>
</tr>
</tbody>
</table>

**Conclusion**

The rate of electrophilic aromatic substitution reactions depends on the reactivity of the electrophile, and steric considerations. The substrate under study is acidic and a weak nucleophile. The electrophile is moderately strong and the bulkiness of the incoming iodo group offers moderate steric hindrance. These factors in unison slow down the iodination rate in comparison with bromination of salicylic acid by bromine in aqueous medium. These facts have been quantitatively justified in the present study.

**References**

RAPID IODINATION OF THE ISOMERS OF AMINOBENZOIC ACID IN AQUEOUS MEDIUM BY IODINE MONOCHLORIDE USING HYDRODYNAMIC VOLTAMMETRY: REGIOSPECIFICITY EFFECT

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Abstract

The rapid kinetics of the iodination of para-aminobenzoic acid and meta-aminobenzoic acid by iodine monochloride at 4.5 pH has been studied by employing hydrodynamic voltammetry. The reactions were found to be of the second order and the specific reaction rates for the two reactions were found to be 25 M^{-1}s^{-1} and 10 M^{-1}s^{-1} at 25.0°C respectively. These data were complemented with those for the iodination of ortho-aminobenzoic acid by ICI obtained earlier to quantitatively assess the relative reactivity of the three isomers stemming from substituent regiospecificity.

Keywords: Iodine monochloride, hydrodynamic voltammetry, aminobenzoic acid isomers.

Introduction

Iodine monochloride is an interhalogen compound with the formula ICl (Lee, 1996). It is polar and is a potential source of I⁻. Iodinations of aromatic substrates in aqueous medium yield iodo derivatives of the substrates that have significance in pharmacodynamics as motifs of drugs having several antiseptic, disinfectant, antiviral and anti-bacterial properties.

The rapidity of halogenations of aromatic substrates in aqueous medium necessitate the use of special techniques to measure the reaction rates (Hernandes, 2010, Borkar, 2013, Dangat et al., 2012). These include temperature jump, stopped flow and pulse radiolysis techniques.

We have herein adopted a relatively simple but efficient technique, hydrodynamic voltammetry, to monitor the rate of the fast iodination of para-aminobenzoic and meta-aminobenzoic acid by iodine monochloride in aqueous solution.

The reactions studied are as follows:

1. \[ \text{H}_2\text{N}-\text{COOH} + \text{ICI}_{\text{aq}} \rightarrow \text{H}_3\text{N}-\text{COOH} + \text{H}^+ + \text{Cl}^-_{\text{aq}} \]
   \[ \text{m-aminobenzoic acid} \]

2. \[ \text{H}_2\text{N}-\text{COOH} + \text{ICI}_{\text{aq}} \rightarrow \text{H}_3\text{N}-\text{COOH} + \text{H}^+ + \text{Cl}^-_{\text{aq}} \]
   \[ \text{p-aminobenzoic acid} \]
Iodine monochloride being the only species in the reaction that is electroactive at a microelectrode, its decay as the reaction proceeds is monitored by determining the nanocurrent at a platinum microelectrode that rotates at 600 rpm. The following are the half-cell reactions at the two electrodes in the galvanic cell used in this hydrodynamic voltammetry technique.

At the positive electrode, RPE

At the negative electrode, SCE

Overall reaction

\[
\begin{align*}
\text{ICI} + 2e^- & \rightarrow \text{I}^- + \text{Cl}^- \\
2\text{Hg} + 2\text{Cl}^- & \rightarrow \text{Hg}_2\text{Cl}_2 + 2e^- \\
\text{ICI} + 2\text{Hg} + 2\text{Cl}^- & \rightarrow \text{Hg}_2\text{Cl}_2 + \text{I}^- + \text{Cl}^- \\
\end{align*}
\]

The use of a large concentration of KCl ensures linear proportionality of the diffusion limited nanocurrent at the RPE generated by iodine monochloride.

**Preparation of solutions**

**Iodine monochloride:** A stock solution of iodine monochloride is prepared in double distilled water. The strength of this solution is determined iodometrically.

A.R. grade aminobenzoic acid isomers and KCl and are used to prepare the stock solutions in water.

**Experimental**

**Instrumentation**

A constant potential of + 0.2 V versus the SCE is applied at the RPE, using a potentiometer.

A galvanometer with the sensitivity of 0.10 nA cm\(^{-1}\) provided with a lamp and scale arrangement is employed to register the nanocurrent due to iodine monochloride. The current passing through the galvanometer is controlled by employing a shunt.

**Calibration of readings**

The two electrodes are dipped in 50.0 cm\(^3\) of 8 \(\times\) 10\(^{-2}\) M KCl, which is the supporting electrolyte at 25.0°C. A potential of + 0.2 V versus the reference electrode is applied at the rotating platinum cathode. The galvanometer light spot is adjusted to zero deflection on the scale. KCl solution is then replaced by 8 \(\times\) 10\(^{-4}\) M iodine monochloride solution containing 8 \(\times\) 10\(^{-4}\) M potassium chloride and the diffusion current reading is set at about 50.0 cm using a shunt. The nanocurrent due to iodine monochloride in the range 2.0 \(\times\) 10\(^{-4}\) M to 8.0 \(\times\) 10\(^{-4}\) M is then recorded without disturbing the shunt for different ICI concentrations.[Table 1]. The plot of [ICI] versus diffusion current is found to be linear.

The temperature of 25.0°C is maintained by the use of a thermostat having 0.10 °C accuracy.

**Kinetic measurements**

25 cm\(^3\) each of 1.6 \(\times\) 10\(^{-3}\) M para-aminobenzoic acid and iodine monochloride, both containing 0.16 M KNO\(_3\) and the required buffers for 4.5 pH are maintained in a thermostat in separate flasks. The contents of the two flasks are mixed in the reaction vessel containing the electrodes, and stop-clock is simultaneously started. The reducing nanocurrent due to ICI is monitored.

The above procedure of calibration and kinetic measurement is repeated for checking the reproducibility of the galvanometer measurements, and these are found to be within the limits of 0.2 cm.

From the deflections noted during the kinetic study, the unconsumed iodine monochloride, is determined using the calibration plot. A graph of [ICI] \(^{-1}\) i.e. 1/(a-x) versus 't' is a straight line ascertaining the order of the reaction to be two.

The gradient of this plot gives the specific reaction rate \(k'\).

The kinetic measurements are repeated for the meta-aminobenzoic acid isomer.

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**Table 1.** Calibration of the diffusion current at 25.0°C

<table>
<thead>
<tr>
<th>[ICI] / 10(^{-4})M</th>
<th>Deflection / nA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>6.3</td>
</tr>
<tr>
<td>2.0</td>
<td>12.6</td>
</tr>
<tr>
<td>4.0</td>
<td>25.1</td>
</tr>
<tr>
<td>6.0</td>
<td>36.2</td>
</tr>
<tr>
<td>8.0</td>
<td>50.0</td>
</tr>
</tbody>
</table>
Results and Discussion

Both the reactions under study are found to follow second order kinetics as the plot of $[\text{ICI}]^V$ vs time is a straight line in each of these two cases the slopes of which yield the specific reaction rates for the iodination of the two isomers under study. A typical observation table is shown in Table 3. The predominant iodinating species in this study is ICI since the hydrolysis of ICI to hypiodous acid is suppressed at pH 4.5 and also due to the large concentration of the KCl used as the supporting electrolyte. The specific reaction rates for the iodination of the three regioisomers are depicted in Table 4. The 3-iodo derivative is the product in both the reactions under study. This is confirmed from NMR characterization.

Table 4: The relative reactivity of the isomers of aminobenzoic acid from kinetic data

<table>
<thead>
<tr>
<th>Regioisomer</th>
<th>Velocity constant for iodination $/\text{M}^{-1}\text{s}^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p$-aminobenzoic acid</td>
<td>25</td>
</tr>
<tr>
<td>$m$-aminobenzoic acid</td>
<td>10</td>
</tr>
<tr>
<td>$o$-aminobenzoic acid</td>
<td>395</td>
</tr>
</tbody>
</table>

Conclusion

The rate of electrophilic aromatic substitution reactions depends on the reactivity of the electrophile and steric considerations. The substrate under study is acidic and a weak nucleophile. The electrophile ICI is moderately strong and the bulkiness of the incoming iodo group offers moderate steric hindrance. The amino group is otho and para directing while the COOH group is meta directing. These factors coupled with steric compulsions of the reaction dynamics, in unison slow down the iodination rate in the meta isomer in comparison with the ortho isomer, the para isomer being moderately reactive. These facts have been quantitatively justified through investigations of the rapid kinetics in the present study.

Green chemistry principles were inherent in the study in view of the short half-lives of the reactions and very low concentrations of the solutions used.
References