Iodination of Salicylamide

Electrophilic Aromatic Substitution

Aromatic compounds are unusually stable because of the delocalization of their π-electrons. Given that the π cloud is so stable, aromatic compounds (like benzene and its derivatives) do not undergo electrophilic addition reactions as simple alkenes do.

\[
\begin{align*}
\text{alkene} & \quad \xrightarrow{\text{Br}_2} \quad \text{no reaction} \\
\text{benzene} & \quad \xrightarrow{\text{Br}_2} \quad \text{no reaction}
\end{align*}
\]

However, the π electrons of aromatic compounds are strongly attracted to powerful electrophiles. When such electrophiles are attacked by the π cloud, the result is a positively charged reactive intermediate known as a sigma (σ) complex.

If the σ complex subsequently reacts with a nucleophilic species, the result would be an addition product, but a loss of aromaticity. This type of reaction does **not** occur in aromatic systems. Instead, a proton (H⁺) is removed from the sigma complex by a base in order to reform the stable aromatic π system. The resulting product is classified as a substitution product since the electrophile substituted for a hydrogen on the ring. This type of reaction is known as an **electrophilic aromatic substitution**.

As shown in the figure below, the sigma complex intermediate is a resonance-stabilized carbocation. The various resonance contributors show that the positive charge is more greatly concentrated on certain carbon atoms.
The delocalization of the positive charge on the sigma complex means that substituents on the ring will affect the reactivity of the ring toward electrophilic aromatic substitution. In fact, substituents affect the ring’s reactivity in a couple of ways. First, electron donating substituents make the ring more susceptible to attack since the resulting sigma complex would be more stable (donating electrons to a carbocation increases its stability) and, therefore easier to form. As you can imagine, electron withdrawing substituents have the opposite effect. In addition, the electronic nature of a substituent also determines where on the ring, relative to the position of the substituent, that an electrophile will attach. These latter effects are termed directing effects, and substituents are grouped according to whether they are ortho, para directors (typically electron donors) or meta directors (typically electron withdrawers).

In this experiment, we will study the directing effects of a pair of substituents on a single aromatic ring. Salicylamide (see structure below), is a component of some analgesics. The hydroxyl group on the ring is a strongly activating, electron donating substituent, while the amide group is electron withdrawing.

The electrophile that we will use is formed from the reaction of sodium hypochlorite (NaOCl, bleach) with iodide ion. The $I^+$ ion formed in this reaction is a strong electrophile that reacts quickly in an electrophilic aromatic substitution reaction.

$$\text{NaOCl} + \text{NaI} \rightarrow I^+$$

Determining Substitution Patterns using IR

The advent of modern technology such as FT-NMR and the recent advances in mass spectrometry have relegated infrared spectroscopy to the task of functional group identification in organic compounds. While this is an important piece of information in organic structural determinations, IR can also provide a wealth of additional information about an organic compound. Unfortunately, this information remains largely untapped because it is buried in the nuances of what is known as the “fingerprint region” of the IR spectrum.

In this experiment, you will be introduced to the use of the fingerprint region of the IR spectrum to determine the substitution pattern of aromatic rings. The spectral region between $700 – 900 \text{ cm}^{-1}$ contains a great deal of useful information for this task. As the following table demonstrates, IR enables us to easily differentiate a variety of substitution patterns on aromatic rings. Given that your job in this lab is to determine where on the ring the iodine substitution occurs, you should find IR a very useful technique!

Your Tasks: 1) Predict the product of the electrophilic iodination of salicylamide (see Question #1 at the end of the lab), 2) synthesize and purify (recrystallize) the product, 3) collect an IR spectrum, interpret it, and determine if your prediction is correct (see Question #5 at the end of the lab).
Fingerprint Infrared Absorptions for Substituted Aromatics

<table>
<thead>
<tr>
<th>Ring substitution pattern*</th>
<th>Expected peaks (cm⁻¹)</th>
<th>Substitution Pattern Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monosubstituted</td>
<td>770 – 715 (strong)</td>
<td><img src="image" alt="Monosubstituted" /></td>
</tr>
<tr>
<td>1,2-Disubstituted</td>
<td>770 – 730 (strong)</td>
<td><img src="image" alt="1,2-Disubstituted" /></td>
</tr>
<tr>
<td>1,3-Disubstituted</td>
<td>820 – 760 (strong)</td>
<td><img src="image" alt="1,3-Disubstituted" /></td>
</tr>
<tr>
<td>1,4-Disubstituted</td>
<td>870 – 800 (strong)</td>
<td><img src="image" alt="1,4-Disubstituted" /></td>
</tr>
<tr>
<td>1,2,3-Trisubstituted</td>
<td>790 – 750 (strong)</td>
<td><img src="image" alt="1,2,3-Trisubstituted" /></td>
</tr>
<tr>
<td>1,2,4-Trisubstituted</td>
<td>850 – 800 (strong)</td>
<td><img src="image" alt="1,2,4-Trisubstituted" /></td>
</tr>
<tr>
<td>1,3,5-Trisubstituted</td>
<td>910 – 830 (strong)</td>
<td><img src="image" alt="1,3,5-Trisubstituted" /></td>
</tr>
</tbody>
</table>

*The numbers here apply to substitution patterns, not nomenclature.

Experimental Procedure

CAUTION: Use caution when handling the materials used in this experiment. Wear gloves and appropriate eye protection at all times during this procedure. Salicylamide and sodium iodide are irritants. Sodium hypochlorite and hydrochloric acid are irritants and are corrosive.

Measure out ~1.0 g of salicylamide and record the mass to the nearest 0.1 g. Place the salicylamide into a 100-mL round-bottom flask. Dissolve the salicylamide in 20 mL of absolute ethanol, warming the flask with your hand to speed up the dissolution.

Once the salicylamide is completely dissolved, add 1.2 g of sodium iodide (NaI) to the reaction mixture, stirring with a glass stirring rod until the solution is homogeneous.

Place the 100-mL round-bottom containing the reaction mixture into an ice bath. (Think about thermal contact!! Ice bath means ice AND water.)

When the reaction is cooled to 0 °C (about 5 minutes), remove the reaction vessel from the ice bath and quickly add 9.2 mL of 6% (w/v) sodium hypochlorite solution (ultra strength household bleach). Swirl the flask vigorously to completely mix the contents. The solution will change colors from the initial clear reaction mixture to a dark red-brown to increasingly lighter shades of yellow. When the solution reaches a faint, pale yellow color, the reaction is complete. (Typically, this takes less than five minutes.) Allow the reaction vessel to sit on the benchtop undisturbed for 10 minutes.

Add 10 mL of a previously prepared solution of 10% (w/v) sodium thiosulfate to the reaction solution and swirl the flask until the contents are thoroughly mixed. Next, acidify
the reaction solution by slowly adding 10% HCl. Monitor the acidity of the solution using litmus paper. You will notice a white solid beginning to form in the reaction vessel. At this point, the pH of the solution is near the desired acidity. Continue adding 10% HCl, but carefully monitor the acidity.

Once the mixture is acidic, filter using vacuum filtration and a Büchner funnel. Collect the precipitate from the filter paper and recrystallize from 95% ethanol. (After the recrystallization mixture has cooled to room temperature, place it in an ice bath for ~15 minutes to complete crystallization.) Filter using vacuum filtration and allow the crystals to remain on the funnel with air being drawn over them for 20 minutes to speed up the drying process.

Once your product is dry, weigh it and collect an IR spectrum using the SMARTPerformer ATR accessory on the spectrophotometer. (Ask your TA for help with the latter.) Be sure to carefully label all peaks between 700 – 900 cm\(^{-1}\) on your spectrum.

### Experimental Record

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass of salicylamide used</td>
<td>________ g</td>
</tr>
<tr>
<td>Moles of salicylamide used</td>
<td>________</td>
</tr>
<tr>
<td>Moles of sodium iodide used</td>
<td>________</td>
</tr>
<tr>
<td>Moles of sodium hypochlorite used</td>
<td>________</td>
</tr>
<tr>
<td>Mass of recrystallized product</td>
<td>________</td>
</tr>
</tbody>
</table>

### Questions

1. Use your knowledge of electrophilic aromatic substitution and the directing effects of substituents on an aromatic ring to answer the following questions.
   
   A. What are the possible sites of iodination of the salicylamide ring? Briefly explain.

   B. Predict the most likely site of iodination of the salicylamide ring and explain your prediction.

2. What is the limiting reagent in this procedure for the iodination of salicylamide?
3. Calculate the theoretical and percent yield of iodinated salicylamide (product) assuming a monoiiodination reaction. (Show your calculations.)

4. The IR spectrum of salicylamide, your starting material, is shown below.
   A. Identify the significant absorbances in the functional group region of the spectrum (above 1400 cm\(^{-1}\)) and correlate each to the structure of salicylamide.

   B. Identify the peak in the fingerprint region that is indicative of the substitution pattern of the aromatic ring of salicylamide.

5. Using the information you collected on the compound that you synthesized, draw the structure of the product. Explain how the data you collected confirms the structure you've proposed.