The Reaction of Salicylaldehyde and Aniline

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Introduction
Aldehydes and ketones show a high degree of reactivity with respect to nucleophilic attack of the carbonyl carbon. Ammonia and its derivatives such as primary amines, hydrazine (N₂H₄) or phenylhydrazines (C₆H₅NHNH₂) all react by initially attacking the carbonyl carbon, followed by hydrogen transfers to give an amine where the nitrogen is bonded to a carbon that also contains a hydroxyl group. Under acidic conditions, the hydroxyl group is protonated, followed by loss of water to give the conjugate acid of the observed product.

\[ R'C'O - R' + NH₂R'' \rightarrow \overset{H-B}{\text{R'C'–OH}} + \overset{H-B}{\text{R''}} \]

\[ \overset{\text{"Schiff Base" or also known as an "imine"}}{\text{R'C'N–R''}} \]

Hydrogen ion transfer then gives the Schiff base product. The condensation step to give water is acid catalyzed and is the rate-determining step of the sequence.

All of the steps of the above sequence are reversible. In principle, the reaction of water with the Schiff base will give back the aldehyde or ketone and the amine from which it was formed. However, here, we are using aromatic reagents, which form products that are more stable than analogous alkyl-containing reagents. Ketones do not react as readily as do aldehydes.

Importance of Imines
From a synthetic perspective, imines are important in the syntheses of complicated amines. The Schiff base can be reduced with hydrogen to give the amine.

From a biological perspective, imines also play an important role in the chemistry of vision: 11-cis-retinal is bonded to opsin (the entire complex is called rhodopsin) by the formation of an imine with the NH₂ of an amino acid residue of the opsin protein. The cis linkage of cis-retinal isomerizes when struck by a photon to form the trans-isomer. The trans isomer does not fit as well in the pocket formed by the opsin, thus the imine linkage hydrolyzes to give the trans-retinal and opsin. Enzymatic isomerization gives back the cis isomer, and the cycle is ready to begin again.

Precautions
Aniline is highly toxic and is an irritant; it is also an anticipated carcinogen. Avoid breathing fumes or fumes from solutions that contain aniline. Wear gloves and keep the reaction in the hood at all times.

**PreLab**

Be sure to include all sections of the PreLab that accompany the Synthetic Experiments. In the Chemical Data Table, you should include your best guess for the structure of the product. The melting point of the product is 51°C (Ref: Dictionary of Organic Compounds, 5th Edition, Volume 3, p. 2992, published by Chapman and Hall, 1982.)

**Questions to be included in your PreLab**

1. More than one geometric isomer is possible for the imine product. Draw them and predict which one will be most favored.
2. Predict the major product of this reaction.
3. How could you determine the ratio of the possible products? For that matter, how could you easily separate the different isomers?

**TLC**

You are required to run a TLC to monitor the progress of the reaction. Plates should have three spots (or lanes) on the origin: one for the main organic starting material that is being transformed, one for a cospot (starting material and the reaction mixture), and one for the reaction mixture.

**Procedure**

To a tared 13 x 100 test tube, add 2.05 mmoles of salicylaldehyde and 2.00 mmol of aniline. Add 1.0 mL of ethanol and 3 boiling chips. Add 1 drop of 5% HCl solution. (If it is not available, make a small amount of your own by mixing 0.1 mL of 10% HCl and 0.1 mL of water.) Gently reflux the mixture for 1 hr. After 1 hr, add another 1.0 mL of ethanol, transfer the liquid to a fresh test tube (leaving the boiling chips behind) and let the mixture cool to room temperature. Place the tube in an ice water bath for 10 min. Once it is very cold, add one small chunk of ice (it has to be small to go into the test tube) and scratch the inner wall of the test tube. Keep the tube chilled and continue to add a few more small chunks of ice. (This step allows the water content of the solution to slowly increase, rather than the sudden change that occurs when water is added; it also helps to chill the solution.) Once crystals begin to form, let the mixture stand for another 5 minutes in ice water. Filter the product using pipet filtration. Wash the solid twice with 1 mL of water. Save a small portion of the crude product for TLC analysis.

**Recrystallization**

The product can be recrystallized from ethanol and water or by dissolving in a minimum of warm ethanol and increasing the water content by dropwise addition of water with intermittent scratching the inside walls of the container with a stir rod. Once all the liquid has been removed, dump the pasty solid onto a piece of filter paper and allow the solid to dry thoroughly before it is weighed, the melting point obtained, and the product analyzed. Analyze the crude product and the recrystallized product by TLC. Include the TLC plates in your Final Report.

**Cleaning Up**

Dispose of all filtrates and wastes in the non-halogenated organic waste containers.

**Analyses**

In addition to TLC analysis, the product may be analyzed by IR, NMR, or MS; see your assignment strip for the specific analysis you are assigned. Analyze your sample according to your Assignment sheet and the instructions on Sample Preparation in Lab Guide. If you analyze the product by IR, the C=N stretch common to imines appears between 1615 and 1700 cm⁻¹; note also that conjugation will shift the absorbance to lower wavenumbers, just as the case with C=O stretching when the carbonyl is conjugated.

**Questions to be answered in the Final Report**
1. Use Aldrich to determine the structure of 1,2-phenylenediamine. Predict the structures of the products that form from the reactions of one mole of 1,2-phenylenediamine and 
a. one mole of salicylaldehyde  
b. two moles of salicylaldehyde  
2. Use resonance structures of your product to rationalize the decreased wavenumber of absorbance of the C=N stretch of a conjugated imine.  
3. The melting point of the product of 4-hydroxybenzaldehyde and aniline is higher than the melting point of the product obtained here from 2-hydroxybenzaldehyde (salicylaldehyde) and aniline. Explain. (It may help to build a molecular model of these.)