Prelab Exercise

Give the detailed mechanism for the synthesis of isobutyl formate by Fischer esterification.

Introduction

The ester group is an important functional group that can be synthesized in a number of different ways. The low-molecular-weight esters have very pleasant odors and indeed are the major components of the flavor and odor aspects of a number of fruits. Although the natural flavor may contain nearly a hundred different compounds, single esters approximate the natural odors and are often used in the food industry for artificial flavors and fragrances. For example, \( n \)-butyl acetate is an ester that is characterized as a strong aroma and flavor in apples. In this experiment, you will be synthesizing this fruity ester.

Esters can be prepared by the reaction of a carboxylic acid with an alcohol in the presence of a catalyst such as concentrated sulfuric acid, hydrogen chloride, \( p \)-toluenesulfonic acid, or the acid form of an ion exchange resin:

\[
\text{H}_3\text{C} \cdot \text{C} \cdot \text{O} \cdot \text{H} + \text{CH}_3\text{OH} \xrightarrow{\text{H}^+} \text{H}_3\text{C} \cdot \text{C} \cdot \text{O} \cdot \text{CH}_3 + \text{H}_2\text{O}
\]

This Fischer esterification reaction reaches equilibrium after a few hours of refluxing. The position of the equilibrium can be shifted by adding more of the acid or of the alcohol, depending on cost or availability. The mechanism of the reaction involves initial protonation of the carboxyl group, attack by the nucleophilic hydroxyl, a proton transfer, and loss of water followed by loss of the catalyzing proton to give the ester. Because each of these steps is completely reversible, this process is also, in reverse, the mechanism for the hydrolysis of an ester:

\[
\begin{align*}
\text{H} & \xrightarrow{+ \text{H}^+} \text{H} \\
\text{R} & \xrightarrow{- \text{H}^+} \text{R} \\
\text{H} & \xrightarrow{+ \text{R}^+} \text{R} \\
\text{H} & \xrightarrow{- \text{R}^+} \text{R} \\
\text{H} & \xrightarrow{- \text{R}^+} \text{R} \\
\text{R} & \xrightarrow{+ \text{H}^+} \text{R} \\
\text{H} & \xrightarrow{+ \text{H}^+} \text{H} \\
\text{R} & \xrightarrow{- \text{H}^+} \text{R} \\
\end{align*}
\]

Other methods are available for the synthesis of esters, most of them more expensive but readily carried out on a small scale. For example, alcohols react with acid anhydrides to form esters:
Acid chlorides form esters by reaction with alcohols:

\[
\text{CH}_3\text{CH}_2\text{OH} + \text{H}_3\text{C}-\text{C}=(\text{Cl})\text{C}-\text{C}=(\text{CH}_3) \xrightarrow{\text{H}^+} \text{CH}_3\text{CH}_2\text{O} \cdot \text{C} \cdot \text{C} \cdot \text{CH}_3 + \text{HCl}
\]

1-Propanol
Acetyl chloride
n-Propyl acetate

In the above reaction, an organic base such as pyridine is usually added to react with the hydrogen chloride.

A number of other methods can be used to synthesize the ester group. Among these are the addition of 2-methylpropene to an acid to form t-butyl esters, the addition of ketene to make acetates, and the reaction of a silver salt with an alkyl halide.

As noted above, Fischer esterification is an equilibrium process. Consider the reaction of acetic acid with 1-butanol to give n-butyl acetate:

\[
\text{H}_3\text{C}-\text{C}=(\text{OH}) + \text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \xrightarrow{\text{H}^+} \text{H}_3\text{C}-\text{C}=(\text{OH})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 + \text{H}_2\text{O}
\]

n-Butylacetate

The equilibrium expression for this reaction is shown below.

\[
K_{eq} = \frac{[\text{H}_3\text{C}-\text{C} \cdot \text{O} \cdot \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3]}{[\text{H}_3\text{C}-\text{C}=(\text{OH})][\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_3]}
\]

For primary alcohols reacting with unhindered carboxylic acids, $K_{eq} \approx 4$. If equal quantities of 1-butanol and acetic acid are allowed to react, the theoretical yield of ester is only 67% at equilibrium. To upset the equilibrium we can, by Le Chatelier's principle, increase the concentration of either the alcohol or acid, as noted above. If either one is doubled, the
theoretical yield increases to 85%. When one is tripled, it goes to 90%. But note that in the example cited the boiling point of the relatively nonpolar ester is only about 8°C higher than the boiling points of the polar acetic acid and 1-butanol, so a difficult separation problem exists if either starting material is increased in concentration and the product is isolated by distillation.

Another way to upset the equilibrium is to remove water. This can be done by adding to the reaction mixture molecular sieves, an artificial zeolite, which preferentially adsorb water. Most other drying agents, such as anhydrous sodium sulfate or calcium chloride, will not remove water at the temperatures used to make esters.

A third way to upset the equilibrium is to preferentially remove the water as an azeotrope. The information in the table below can be found in any chemistry handbook table of ternary (three-component) azeotropes.

### The Ternary Azeotrope of Boiling Point 90.7°C

<table>
<thead>
<tr>
<th>Compound</th>
<th>Boiling Point of Pure Compound (°C)</th>
<th>Vapor Phase</th>
<th>Upper Layer</th>
<th>Lower Layer</th>
</tr>
</thead>
<tbody>
<tr>
<td>l-Butanol</td>
<td>117.7</td>
<td>8.0</td>
<td>11.0</td>
<td>2.0</td>
</tr>
<tr>
<td>n-Butyl acetate</td>
<td>126.7</td>
<td>63.0</td>
<td>86.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Water</td>
<td>100.0</td>
<td>29.0</td>
<td>3.0</td>
<td>97.0</td>
</tr>
</tbody>
</table>

These data tell us that the vapor that distills from a mixture of 1-butanol, *n*-butyl acetate, and water will boil at 90.7°C and the vapor contains 8% alcohol, 63% ester, and 29% water. The vapor is homogeneous, but when it condenses, it separates into two layers. The upper layer is composed of 11% alcohol, 86% ester, and 3% water, but the lower layer consists of 97% water with only traces of alcohol and ester. If some ingenious way to remove the lower layer from the condensate and still return the upper layer to the reaction mixture can be devised, then the equilibrium can be upset and nearly 100% of the ester can be produced in the reaction flask.
A Modified Dean-Stark Apparatus

Dean-Stark Apparatus
The apparatus shown above, a modified Dean-Stark apparatus/trap, achieves the desired separation of the two layers. The mixture of equimolar quantities of 1-butanol and acetic acid is placed and stirred in the flask along with an acid catalyst. The azeotropic vapor distills at 90.7°C and condenses and runs down to the sidearm of the 3-way connector; this sidearm is closed with a cork. The layers separate, with the denser water layer remaining in the sidearm while the lighter n-butyl acetate/ethanol layer (organic layer) runs down into the reaction flask. As soon as the theoretical quantity of water has collected, the reaction is over and the product in the flask should be ester of high purity.

Esterfication using a carboxylic acid and an alcohol requires an acid catalyst. In this experiment, the acid form of an ion-exchange resin is used. This resin, in the form of small beads, is a cross-linked polystyrene that bears sulfonic acid groups on some of the phenyl groups. Essentially it is an immobilized form of p-toluenesulfonic acid, an organic-substituted sulfuric acid; see figure below. This catalyst has the distinct advantage that at the end of the reaction it can be removed simply by filtration. Immobilized catalysts of this type are becoming more and more common in organic synthesis.
**Synthesis of n-Butyl Acetate by Azeotropic Distillation of Water**

\[
\begin{align*}
\text{CH}_3\text{COOH} & \quad + \quad \text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\
\text{Acetic acid} & \quad \text{MW 60.05 bp 117.9°C,} \\
\text{MW 60.05 bp 117.9°C,} & \quad \text{den 1.049} \\
\text{den 1.049} & \quad \text{n}_D^{20} 1.3720 \\
\text{1-Butanol.} & \quad \text{MW 74.12 bp 117.7°C,} \\
\text{MW 74.12 bp 117.7°C,} & \quad \text{den 0.810} \\
\text{den 0.810} & \quad \text{n}_D^{20} 1.3990 \\
\text{H}^+ & \quad \text{CH}_3\text{O} \quad \text{O-CO-CH}_2\text{CH}_2\text{CH}_3 \quad + \quad \text{H}_2\text{O} \\
n-\text{Butyl acetate} & \quad \text{MW 116.16} \\
\text{MW 116.16} & \quad \text{bp 126.5°C, den 0.882} \\
\text{den 0.882} & \quad \text{n}_D^{20} 1.3940
\end{align*}
\]

Prepare 0.2 g of Dowex 50X2-100 ion-exchange resin. Wash the resin with water and remove water by decantation, which removes much of the yellow color. Collect the resin by vacuum filtration on a Buchner funnel. Now it’s ready for use in the reaction.

In a 5-mL short-necked round-bottomed flask, place 0.2 g of Dowex 50X2-100 ion-exchange resin, 0.61 g (0.58 mL) of acetic acid, 0.74 g (0.91 mL) of 1-butanol, and a 1/2” stirring bar. Set up the Dean-Stark trap as shown above by attaching the 3-way connector, with the sidearm corked (see the modified Dean-Stark apparatus figure above). Connect an empty air condenser (distilling column) to the 3-way connector and clamp the apparatus at the angle shown. Heat the flask with stirring on a hot sand bath, and boil the reaction mixture. (Stirring the mixture prevents it from bumping.) As an option, you might hold a thermometer just above the boiling liquid and note a temperature of about 91°C. Remove the thermometer and allow the reaction mixture to reflux in such a manner that the vapors condense about one-third of the way up the empty distilling column, which is functioning as an air condenser. Note that the material that condenses is not homogeneous, since droplets of water begin to collect in the upper part of the apparatus. As the sidearm fills with condensate, it is cloudy at first and then two layers separate. When the volume of the lower aqueous layer (in the sidearm of the 3-way connector) does not appear to increase, the reaction is over. This will take about 20 to 30 minutes.

**Isolation and Purification**

First, tare a 20-mL vial. Next, carefully lift the apparatus from the sand bath, not changing its slanted position, and allow it to cool. Tip the apparatus very carefully allowing the upper layer, which contains the ester and alcohol, to run back into the reaction flask. When doing this, make sure that the lower water layer remains in the side arm and does not run back into the reaction flask. Disconnect the flask and remove the product from it with a Pasteur pipette transferring it to the tared vial, and determine its weight. Analyze the product by the method on your assignment sheet using the instructions in the Lab Guide for preparing the sample.

**Analysis**

You will be instructed to analyze your final product by IR or NMR. Analyze your sample according to your Assignment sheet and prepare it as per the instructions on Sample Preparation in Lab Guide.
Cleaning Up
After drying, place the catalyst in the solid waste bin.

Post Lab Questions
1. Write a balanced equation for the saponification of glycerol tristearate with excess NaOH.

\[
\begin{align*}
\text{CH}_2 - \text{O} - \text{C} - (\text{CH}_3)_{16} \text{CH}_3 \\
\text{HC} - \text{O} - \text{C} - (\text{CH}_3)_{16} \text{CH}_3 \\
\text{CH}_3 - \text{O} - \text{C} - (\text{CH}_3)_{16} \text{CH}_3
\end{align*}
\]

Glycerol Tristearate
mp 69.9°C
MW 891.52

2. What would happen if the ester you made was heated with a large volume of ethanol containing some sulfuric acid?

3. Fischer esterification is not useful for most tertiary alcohols. Explain.

4. What evidence do you have that the ester should float on water? Explain.