Experiment 23

Analysis of Aspirin

GOALS:
This is the second of two weeks related to aspirin. Last week you made and purified aspirin. This week you will use NMR, IR, and melting point to characterize your product.

INTRODUCTION:
Recall that last week you did the reaction shown to prepare aspirin. You saved a small amount of your crude product and then recrystallized the rest to purify it.

Preparation of acetylsalicylic acid

\[
\begin{array}{c}
\text{H} \\
\text{C} \text{C} \text{C} \\
\text{H} \\
\text{H} \\
\text{C} \text{C} \text{C} \\
\text{O} \\
\text{H} \\
\text{H} \\
\text{C} \text{C} \text{C} \\
\text{O} \\
\end{array} + \begin{array}{c}
\text{H}_2\text{C} \text{C} \text{O} \\
\text{H}_2\text{C} \text{C} \text{O} \\
\end{array} \xrightarrow{\text{H}^+} \begin{array}{c}
\text{H} \\
\text{C} \text{C} \text{C} \\
\text{H} \\
\text{H} \\
\text{C} \text{C} \text{C} \\
\text{O} \\
\text{C} \text{O} \\
\text{H} \\
\text{H} \\
\text{C} \text{C} \text{C} \\
\text{O} \\
\end{array} + \begin{array}{c}
\text{H}_2\text{C} \text{C} \text{O} \\
\text{H} \\
\end{array}
\]

salicylic acid   acetic anhydride   acetylsalicylic acid (aspirin)   acetic acid

This week you will characterize your aspirin product by melting point, IR, and \(^1\)H NMR. To save to time, you will not run the \(^13\)C NMR. Instead, you will analyze the \(^13\)C NMR spectrum provided on the last page of this handout.

Characterization by Melting Point.
Melting point can give us some very general information about a compound’s purity. Although you are used to seeing single temperatures listed for a melting point, in lab we normally measure a melting point range, from the temperature where crystals first appear to soften to the temperature where they are fully liquid. Pure materials melt in a narrow temperature ranges (less than one degree). Impure compounds usually melt at lower temperatures, and over wider ranges.

Characterization by IR Spectroscopy.
As you learned in an earlier experiment, infrared (IR) radiation interacts with the bonds between the atoms of a molecule. This makes it a good technique to investigate functional groups such as the O-H in alcohols, the C=O in carboxylic acids, etc. The table at right shows IR frequencies for several functional group bond types. Note that some of the ranges overlap.

<table>
<thead>
<tr>
<th>Bond type</th>
<th>Absorption Range, cm(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>O – H</td>
<td>3600-3200 (usually broad)</td>
</tr>
<tr>
<td>C – H</td>
<td>3300-2800</td>
</tr>
<tr>
<td>C = N</td>
<td>2260-2220</td>
</tr>
<tr>
<td>C = O</td>
<td>1800-1630 (usually strong)</td>
</tr>
</tbody>
</table>

Characterization by NMR Spectroscopy.
Another spectroscopic technique we will use is NMR. As you should remember from Experiment 11, NMR spectroscopy depends on the interaction of electromagnetic radiation with nuclei. We look at just one type of nucleus at a time. In \(^13\)C NMR, we see just the carbon atoms in a molecule. In \(^1\)H NMR, we see just the hydrogen atoms in a molecule.
$^{13}$C NMR spectra give simple patterns. Each unique type of carbon atom in a molecule will give a different peak in the spectrum. The position of the peak (chemical shift measured in ppm) gives information about the atoms connected to the carbon atom (its environment). The CDCl$_3$ solvent shows up at 77 ppm and should be ignored. To save some time, the $^{13}$C spectrum of aspirin is attached at the end of this handout. You will need to use that spectrum as part of your lab report. Note that in this reference spectrum, the solvent peak at 77 ppm has been artificially removed.

<table>
<thead>
<tr>
<th>$^{13}$C Peak Position</th>
<th>Type of Carbon</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 40 ppm</td>
<td>CH$_n$, carbon attached by single bonds to only carbon and hydrogen</td>
</tr>
<tr>
<td>40 - 80 ppm</td>
<td>C-Cl or C-O, carbon attached to chlorine or oxygen by single bonds</td>
</tr>
<tr>
<td>100 - 160 ppm</td>
<td>C = C, carbon attached to another carbon by a double bond</td>
</tr>
<tr>
<td>160 - 220 ppm</td>
<td>C = O, carbon attached to an oxygen by a double bond</td>
</tr>
</tbody>
</table>

$^{13}$C NMR Summary
1. number of peaks = number of types of C atoms
2. peak position tells what the C atom is attached to (see Table 1)
3. ignore the CDCl$_3$ solvent peak at 77 ppm

$^1$H NMR spectra give more complicated patterns. While this may be intimidating at first, it also provides much more detailed information. The position of the peak (chemical shift measured in ppm) gives information about the atoms connected to the hydrogen (its environment). The table below shows where different types of hydrogen atoms will appear. Don’t be too rigid in focusing on the ranges. As we saw with the IR spectra, some overlapping of the ranges is possible.

<table>
<thead>
<tr>
<th>Acid/aldehyde</th>
<th>phenyl</th>
<th>On a double bond (vinyllic)</th>
<th>Near electronegative element: Z = O, N, X (halogen)</th>
<th>Next to a double bond (allylic)</th>
<th>Near only single bonds (saturated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>H</td>
<td>C-H</td>
<td>Z</td>
<td>C=C</td>
<td>C=C</td>
</tr>
<tr>
<td>C=O</td>
<td>C=O</td>
<td>H</td>
<td>C=O</td>
<td>C=O</td>
<td>C=O</td>
</tr>
<tr>
<td>C=OH</td>
<td>C=O</td>
<td>H</td>
<td>C=O</td>
<td>C=O</td>
<td>C=O</td>
</tr>
</tbody>
</table>

Correlation Table of Positions of Common Groups in the $^1$H NMR
The integrated area of each peak in the $^1$H spectrum is proportional to the number of hydrogen atoms it represents. Integrated areas are usually printed below the x-axis of the spectrum. If we had four peaks with areas of 12.5, 26, 12, and 37, we would interpret this as a ratio of 1:2:1:3. In other words, we would have a structure with 7 hydrogen atoms, 1 of the first type, 2 of the second type, 1 of the third type, and 3 of the fourth type. What would it mean if we also had a tiny peak integrating as 0.5? Recall that just one hydrogen atom integrated as about 12. This tiny peak can’t be from the same compound. It is too small. It must be from an impurity. We get to ignore it. So, remember that in your $^1$H spectrum, peaks from your compound must be of generally similar size. If you know what your compound is supposed to be (e.g. aspirin), you can look at the structure and predict about how many peaks should be in different areas of the spectrum (ppm values) and also their relative sizes.

$^1$H NMR spectra also exhibit splitting. A single peak can be split into two, three, four, or more closely spaced sections. An unsplit peak is called a singlet. Other peaks will be doublets, triplets, quartets, etc. What determines the splitting pattern? The number of hydrogen atoms on neighboring carbon atoms. Add 1 to the number of neighboring hydrogen atoms and you get the splitting. Recall, for example, that in our first NMR experiment we looked at ethyl groups, $-\text{CH}_2\text{CH}_3$. The three hydrogen atoms on the end carbon will show up in one peak. The two hydrogen atoms on the other carbon atom will show up in a second peak. The integrated ratio of the areas of these peaks will be 3:2 due to the number of hydrogen atoms in each. The splitting patterns come from the neighbors. So, the three hydrogens on the end look at the neighboring carbon and see 2 neighbor hydrogens. 2+1 = 3, so we get a triplet for our end hydrogen atoms. The two hydrogen atoms on the other carbon look out and see 3 neighbor hydrogens. 3+1 = 4, so we get a quartet for our second peak.

### $^1$H NMR Summary

1. number of peaks = number of types of H atoms
2. peak position tells what the H atom is attached to (see correlation table above)
3. area under a peak is proportional to the number of H atoms of that type
4. splitting is caused by H atoms on immediately neighboring carbon atoms
5. “n” neighbors give a splitting into “n+1” peaks
6. hydrogen atoms bonded to oxygen atoms don’t show splitting, and sometimes don’t show up at all.

**HAZARDS:**
The NMR instrument contains a very strong magnet. Persons with pacemakers and metal prosthetic devices can also be harmed, and should not approach closer than five feet from the magnet until it has been determined that a closer approach is not harmful. The CDCl$_3$ solvent is a carcinogen and should be used in a hood. Note that CDCl$_3$ is deuterated chloroform. The $^1$H in CHCl$_3$ has been replaced with deuterium ($^2$H or D) so that it will not give a signal in the $^1$H NMR. We will still a small signal, however, due to some CHCl$_3$ impurity in the CDCl$_3$ solvent.
PROCEDURE FOR THE SECOND WEEK:

Part 3: Yield of your Aspirin
Weigh the final aspirin product. Record this mass and your observations of the product. The mass you record is your “actual yield.”

Part 4: Determination of the Melting Point
1. Wear your goggles while preparing the melting point tubes and while measuring melting point.
2. Prepare one capillary tube with crude aspirin, and a second capillary tube with recrystallized aspirin. Press the open end of a capillary tube into some crystals. You need just one or two very tiny crystals inside the tube. If you can see the crystals, you have enough.
3. Tap the tube lightly on the counter to get the crystals to move to the closed end. If needed, drop the capillary tube through a long piece of glass tubing, as demonstrated by your instructor.
4. Check the thermometer on the melting point apparatus. Be sure that it registers below 100 °C. Place both capillary tubes in the same melting point apparatus. Turn on the power. Note that you can see the capillaries through the eyepiece.
5. Set the power to a middle setting (4 or 5). Watch how quickly the temperature rises. You can allow it to run up to 100 °C fairly quickly. You would like the temperature to be rising just 2-5 °C per minute at the point the sample melts. Adjust the power setting accordingly.
6. As the solid melts, you will be able to see the crystals collapsing. Record a melting point range, starting with the temperature where the crystals seem to first begin to collapse and ending with the temperature where the sample is fully liquid. As soon as your sample melts, immediately turn off the melting point apparatus so that it will begin to cool for the next person.
7. Discard the melting point capillaries in the glass disposal box.

Part 5: Preparation of the NMR Sample and Recording Its Spectrum
1. Wear your goggles while preparing your NMR tube. In the NMR sample preparation area in a hood is an NMR tube containing 15 mg of aspirin that we will be using to estimate the amount of aspirin to place in your tube. Take a clean NMR tube and place an equivalent amount of your recrystallized aspirin product into it.
2. Place your NMR tube inside the solvent measuring tube. Use a disposable pipet to add just enough CDCl₃ so that the level of the solvent in the NMR tube is between the two etched lines on the measuring tube. This is about 3 finger-widths tall in the tube. Place the cap on the NMR tube, and invert it several times to dissolve and mix.
3. Take your NMR sample to the NMR room on first floor (Kolthoff 162) where you will be assisted in obtaining the ¹H spectrum. Note that the ¹³C spectrum is attached to this handout. You will need both for your report.
Part 6: Preparation of the IR Sample and Recording Its Spectrum.

Take the IR spectrum of your recrystallized product in the 5th floor lab. Place a small amount of your sample on the ATR (Attenuated Total Reflectance) crystal plate as directed by your instructor. Turn the knob to lower the clamp until it no longer tightens. You are now ready to scan your sample. After the scan is complete you must clean off the crystal plate. Use a cotton swab and isopropyl alcohol provided near the ATR to clean the crystal plate. Make sure that all of your sample is cleaned from the area.

Once you are sure that you have completed all parts of the experiment, discard your aspirin in the trashcan.

LAB REPORT FOR SECOND WEEK:

Results and Discussion:
Below are specific steps to follow for analyzing your results. Discuss your findings from each part in a well-written discussion section. Some specifics of what to include in this discussion are listed below in the steps for analyzing your results. Don't just answer the questions below in order.

1. Calculate and report your percentage yield. Recall that you calculated the theoretical yield of aspirin for your Week 1 report. You measured the actual yield in lab this week.
2. On your IR spectrum, draw the structure of aspirin. You can find this structure in the Introduction. Now consult the table of IR bond frequencies from the Introduction. Label several peaks on your spectrum that correspond to specific bond types in aspirin. (Most of your peaks will not be labeled.) If your sample has water in it, the O-H region of the spectrum will be very strong and broad. Did you find all the expected types of bonds? Does your sample seem to contain water?
3. Look up the accepted melting point for aspirin (acetylsalicylic acid) in either the Merck Index or the CRC. (These are available in the library or in the Reading Room outside our lab.) Prepare a very small table with this accepted melting point (use a citation to show where you got the value), your experimental melting range for crude aspirin, and your experimental melting point range for recrystallized aspirin. Consider what this data says about the purity of your aspirin. Recall that purer substances melt at higher temperatures and in a narrower range.
4. On the $^{13}$C NMR spectrum from this handout, draw the structure of aspirin.
   a. Recall that every kind of carbon atom in your molecule should give a single line in the $^{13}$C spectrum. Count up the number of types of carbon in your structure. Label each unique carbon atom in your aspirin structure with a letter (A, B, etc) Count up the number of peaks in your spectrum. Do these numbers match?
   b. Now look at the $^{13}$C peak frequency table in the Introduction. Compare your structure with labeled carbon atoms to this table. How many carbon peaks should show up in each region of the spectrum? Describe your comparison of the experimental spectrum to the structure of aspirin and your expectations for the number of peaks in the spectrum. Describe which peaks you can match to specific carbon atoms, which you can narrow down to a particular region, and any that seem to be “missing.”
5. On your $^{1}$H NMR spectrum, draw the structure of aspirin.
   a. Place an X on the solvent peak at 7.2 ppm and label it CHCl$_3$ solvent impurity. Recall that all the peaks in the spectrum due to aspirin should be of generally similar heights and have integrated areas proportional to the number of hydrogen atoms of each type. Focus on the integrated areas. An individual peak from a compound may be 3 or 4 times taller than another peak from that same compound, but not 50 or 100 times taller. The integrated areas provide the most accurate measure of peaks size. For this reason, very short peaks or ones with low integrations are impurities and can be ignored.
b. Recall that every kind of hydrogen atom in your molecule should give a peak but that these peaks may exhibit splitting. Count up the number of types of hydrogen atoms in your structure. Label each unique type of hydrogen atom with a letter (A, B, etc.)

c. Look at the correlation table for $^1$H typical peaks given in the Introduction. Compare your structure with the labeled hydrogen atoms in this table. How many hydrogen peaks should show up in each region of the spectrum?

d. Describe your comparison. Describe which peaks you can match to specific hydrogen atoms. Which can you narrow down to a particular region of the spectrum? Do any of the hydrogen atoms seem to be missing? (Recall that the integrated area of each peak tells you how many hydrogen atoms are on the neighboring carbon atoms. The splitting is always neighbors + 1. Thus, a triplet is caused by having two neighboring hydrogen atoms.) Explain the causes of any splitting you see and the integrated peak areas you find.

6. Overall, what can you say about the purity of your recrystallized aspirin based upon its melting point, IR spectrum, and NMR spectra? Look back at the paragraph you wrote for your week 1 report. Do we see specific evidence for any of the compounds you thought to be likely impurities?

Attach your IR, $^1$H NMR, and $^{13}$C NMR spectra to your report.
Note that this reference spectrum does not show the solvent peaks at 77 ppm that we expect when a spectrum is run in CDCl₃. These have been artificially removed to avoid confusion. Sometimes it is difficult to tell whether you have 1 or 2 peaks without expanding the spectrum. The somewhat thicker line at about 170 ppm is actually 2 peaks at 170.2 and 169.8 ppm. All the other lines in the spectrum above are single peaks.