SYNTHESIS OF ANALGESICS: ASPIRIN & ACETAMINOPHEN

EXPERIMENTAL TECHNIQUES REQUIRED
Recrystallisation (T 2), filtration (T 3), melting point determination (T 4), yield calculation (T 14)

OTHER DOCUMENTS:
Experimental procedures: Synthesis of Aspirin, Synthesis of Acetaminophen
Report templates: Aspirin report, Acetaminophen report

INTRODUCTION
In this two week experiment you will be synthesising and purifying two common analgesics (painkillers) aspirin and acetaminophen. Aspirin is prepared by the O-acylation (i.e. add an acyl group to an oxygen) of salicylic acid. Similarly, acetaminophen is prepared by the N-acylation (i.e. add an acyl group to a nitrogen) of p-aminophenol. Note the similarity between the two reactions. The crude samples will be purified by recrystallisation and the melting points of the products measured as a means of checking their identity and purity.

The purpose of this experiment is to prepare the analgesics (i.e. practice the art of chemical synthesis), to practice the fundamentally important skill of purification by efficient recrystallisation, and apply the previously learned technique of melting point determination. Try to have the two crude products prepared by the end of the first week.

BACKGROUND ON ANALGESICS
Aspirin (acetyl salicylic acid or ASA) is one of the most commonly taken medications yet the mode of action is not yet completely understood. Aspirin is an analgesic (relieves pain), an antipyretic (reduces fever) and an anti-inflammatory (reduces swelling). Studies also suggest that aspirin can also reduce the risk of heart attack. Aspirin was developed in order to avoid the irritation problems associated with salicylic acid, the active ingredient in willow bark whose curative effects have been known since 1763.

N-acylated aromatic amines (those having an acyl group, $R-CO-$, substituted on nitrogen) are important in over-the-counter headache remedies. Over-the-counter drugs are those you may buy without a prescription. Acetanilide, phenacetin, and acetaminophen (see over for structures) are mild analgesics and antipyretics and are important, along with aspirin, in many nonprescription drugs.
The discovery that acetanilide was an effective antipyretic came about by accident in 1886. Two doctors, Cahn and Hepp, had been testing naphthalene as a possible vermifuge (an agent that expels worms). By accident, they mixed up a bottle of acetanilide and the bottle of naphthalene. The patient's worms didn't disappear but his fever did - dramatically.

In another instance of serendipity, the publication of Cahn and Hepp describing their experiments with acetanilide, caught the attention of Carl Duisberg, director of research at the Bayer Company in Germany. Duisberg was confronted with the problem of profitably getting rid of nearly 50 tons of p-aminophenol, a by-product from the synthesis of one of Bayer's other commercial products. He immediately saw the possibility of converting p-aminophenol to a compound similar in structure to acetanilide, by putting an acyl group on the nitrogen. It was then believed, however, that all compounds having a hydroxyl group on a benzene ring (that is, phenols) were toxic. Duisberg devised a scheme of structural modification of p-aminophenol to get the compound phenacetin. The reaction scheme is shown here.

Phenacetin turned out to be a highly effective analgesic and antipyretic. A common form of combination pain reliever, called an APC tablet, was once available. An APC tablet contained Aspirin, Phenacetin, and Caffeine (hence, APC). Phenacetin is no longer used in commercial pain-relief preparations. It was later found that not all aromatic hydroxyl groups lead to toxic compounds, and today the compound acetaminophen is very widely used as an analgesic in place of phenacetin. ‘Acetaminophen’ (4-acetamidophenol) is sold as the over-the-counter analgesic "Tylenol"®.
This synthesis will involve the reaction of two functional groups, an alcohol and an acid anhydride (a carboxylic acid derivative), to form a product, an ester. The ester product will be isolated, and purified by recrystallisation. The efficiency of the recrystallisation will be monitored using a simple functional group test. Salicylic acid (o-hydroxy benzoic acid) reacts with acetic anhydride to form acetyl salicylic acid and acetic acid according to the following equation:

\[
\begin{align*}
\text{salicylic acid} & \quad \text{(o-hydroxy benzoic acid)} \\
+ \quad \text{acetic anhydride} & \quad \text{(an acid anhydride)} \\
\rightarrow \quad \text{acetyl salicylic acid} & \quad \text{(an ester)} \\
+ \quad \text{acetic acid} & \quad \text{(a carboxylic acid)}
\end{align*}
\]

The most likely impurities in the crude acetyl salicylic acid are unreacted salicylic acid and a polymeric ester by-product. The polymeric by-product is not soluble in sodium bicarbonate and can be removed by dissolving the crude product in sodium bicarbonate, filtering to remove the insoluble polymer then acidifying to recover the acetyl salicylic acid.

### Reagents and Products

<table>
<thead>
<tr>
<th>Compound</th>
<th>Name</th>
<th>M.W.</th>
<th>bp/mp</th>
<th>density</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{C}_6\text{H}_4\text{CO}_2\text{H})</td>
<td>salicylic acid</td>
<td>138</td>
<td>m 157-159°</td>
<td>-</td>
</tr>
<tr>
<td>((\text{CH}_3\text{CO}))_2\text{O}</td>
<td>acetic anhydride</td>
<td>102</td>
<td>b 136°/760</td>
<td>1.08 g/mL</td>
</tr>
<tr>
<td>(\text{CH}_3\text{COOH})</td>
<td>acetic acid</td>
<td>60</td>
<td>b 118°/760</td>
<td>1.05 g/mL</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_4\text{CO}_2\text{H})</td>
<td>aspirin</td>
<td>180</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The phenol functional group reacts with ferric chloride to give a complex with a definite colour ranging from red to violet, depending on the particular phenol present. Unlike salicylic acid, pure acetyl salicylic acid has no phenolic -OH and therefore does not give a colour change. Therefore, the presence of contaminating salicylic acid in the crude product can be detected using ferric chloride and removed by recrystallization.
PREPARATION AND PURIFICATION OF ACETAMINOPHEN

\[
\begin{align*}
\text{p-aminophenol} & \quad \text{(an amine)} \\
\text{acetic anhydride} & \quad \text{(an acid anhydride)} \\
\text{acetaminophen} & \quad \text{p-acetamidophenol} \\
& \quad \text{(an amide)} \\
\text{acetic acid} & \quad \text{(a carboxylic acid)}
\end{align*}
\]

This synthesis will involve the reaction of two compounds, an amine and a carboxylic acid derivative, to form a product, an amide. The amide product will be isolated, and purified by recrystallisation.

Reagents and Products

<table>
<thead>
<tr>
<th>Compound</th>
<th>Name</th>
<th>M.W.</th>
<th>bp/mp</th>
<th>density</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{NH}_2 )</td>
<td>p-aminophenol</td>
<td>109</td>
<td>m 188-190(^\circ)</td>
<td>-</td>
</tr>
<tr>
<td>( \text{CH}_3\text{CO})_2\text{O} )</td>
<td>acetic anhydride</td>
<td>102</td>
<td>b 136(^\circ)/760</td>
<td>1.08 g/mL</td>
</tr>
<tr>
<td>\text{CH}_3\text{COOH}</td>
<td>acetic acid</td>
<td>60</td>
<td>b 118(^\circ)/760</td>
<td>1.05 g/mL</td>
</tr>
<tr>
<td>( \text{NHCOCH}_3 )</td>
<td>acetaminophen</td>
<td>151</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

REFERENCES
2) Organic Chemistry etext, [http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch20/ch20-0.html](http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch20/ch20-0.html) [http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch20/ch20-3-2.html](http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch20/ch20-3-2.html)