Work through the ChemCAL modules “Organic Reduction and Oxidation” and “Nucleophilic Addition to Carbonyl Groups”

1. Aspirin, acetylsalicylic acid, is almost insoluble in water and taken (by humans) in pill form. (Note that it is very toxic to cats.) Aspro Clear is water soluble and taken after dissolving it in water. What is the link between chemical structure and solubility in this case?

Aspirin

\[
\begin{array}{c}
\text{Aspirin} \\
\begin{array}{c}
\text{OH} \\
\text{O} \\
\text{O} \\
\end{array}
\end{array}
\]

Aspro Clear

\[
\begin{array}{c}
\text{Aspro Clear} \\
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{Na} \\
\end{array}
\end{array}
\]

2. Treatment of a long chain ‘saturated’ (ie no C=C double bonds) fatty acid with NaOH produces the sodium salt of the carboxylic acid. Why do these molecules act as soaps?

3. An omega-3 fatty acid is a carboxylic acid with a long chain and a double bond at the third carbon atom form the ‘tail’ end. An omega-6 fatty acid has a double bond at the sixth carbon atom from the ‘tail’ end. Both omega-3 and omega-6 fatty acids are classified as essential nutrients; they are required by humans, but must be sourced in our diet as they cannot be synthesised by the body. As our modern diet does not contain as many of these oils as it once did, we are encouraged to eat foods such as fish to ensure we have an adequate supply.

An omega-3 fatty acid

\[
\begin{array}{c}
\text{An omega-3 fatty acid} \\
\begin{array}{c}
\text{HO} \\
\text{O} \\
\end{array}
\end{array}
\]

An omega-6 fatty acid

\[
\begin{array}{c}
\text{An omega-6 fatty acid} \\
\begin{array}{c}
\text{HO} \\
\text{O} \\
\end{array}
\end{array}
\]

So why are ‘unsaturated fats’ important in the body? As depicted on the next page, omega-6 fats like linoleic acid are converted to arachidonic acid which in turn is converted by the enzyme cyclooxygenase (COX) into a cascade of different prostaglandin molecules. (The name was chosen as these compounds were originally isolated from the prostate glands of sheep.) Prostaglandins are involved in many diverse bodily processes. For example, they cause inflammation, lower blood pressure, regulate blood platelet clotting and lower gastric secretions.
linoleic acid, an omega-6 fatty acid

\[
\begin{align*}
\text{HO} & \\
\text{O} & \\
\end{align*}
\]

\[
\begin{align*}
\text{COOH} & \\
\end{align*}
\]

arachidonic acid

\[
\begin{align*}
\text{COOH} & \\
\end{align*}
\]

O\(_2\) and COX enzymes

prostaglandin PGH\(_2\)

one of many produced in the arachidonic acid cascade

What is the molecular formula of PGH\(_2\)? Indicate the stereochemistry (Z/E) of the double bonds in PGH\(_2\).

4. Aspirin inhibits the COX enzyme, blocking prostaglandin synthesis and so may be used to limit inflammation, thereby treating arthritic pain or headache. However, it also stops formation of the prostaglandin that limits production of stomach acid and hence can result in a rise of stomach acidity. While taking a small dose of aspirin before a long flight can help prevent deep vein thrombosis, it should not be taken before surgery – in both cases it reduces blood clotting tendencies.

What part of aspirin do you think binds to COX and so inhibits the function of these enzymes?
5. Omega-3 oils are at the start of another cascade of prostaglandin syntheses however the prostaglandins produced in this case do not have such great inflammatory properties as those from omega 6 fats. Boosting the omega-3 route provides competition and so reduces the effect of the omega-6 derived prostaglandins. Consequently I give my dog fish oil capsules, rich in omega-3 fats, as one part of her arthritis medication!

Do you think α–linoleic acid would make as good a soap as a saturated fat?

6. ‘Trans’ fats are ones in which the double bond has an $E$ configuration. They occur naturally in ruminants such as sheep and cows and are produced when vegetable oils are partially hydrogenated.

The hydrogenation process adds $H_2$ to some of the double bonds and changes the remaining double bonds to the $E$ configuration. ‘Trans’ fats are linked to heart disease and high levels of the ‘bad’ cholesterol.

Draw a stick structure of $E$-elaidic acid.

7. Codeine and paracetamol are common analgesics that are present in a number of readily available analgesic preparations. Many tablets also contain pseudoephedrine, a nasal decongestant.

(a) List the functional groups present in each these three molecules.
(b) Which of these compounds will dissolve in dilute aqueous NaOH? Give the structures of the products that are formed in each case where a reaction occurs.
(c) Which compounds will dissolve in dilute aqueous hydrochloric acid? Give the structures of the products that are formed in each case where a reaction occurs.
(d) Which of the compounds will react with NaNH$_2$?
(e) Which of the compounds will undergo an electrophilic addition reaction to decolourise a solution of bromine water?
8. Lipoic acid (thioctic acid) plays an essential role in biochemical redox processes. Indicate the laboratory reagents and conditions required for the following conversions.

(a) 
\[
\begin{align*}
\text{Cyclic thioester} & \quad \text{Cyclic thioester} \\
\text{SH} & \quad \text{SH} \\
\text{CH}_2 \text{COOH} & \quad \text{CH}_2 \text{COOH}
\end{align*}
\]

(b) 
\[
\begin{align*}
\text{Cyclic thioester} & \quad \text{Cyclic thioester} \\
\text{SH} & \quad \text{SH} \\
\text{CH}_2 \text{COOH} & \quad \text{CH}_2 \text{COOH}
\end{align*}
\]

9. The biological process corresponding to the conversion of dihydrolipoic acid into lipoic acid may be written as

\[
\begin{align*}
\text{Dihydrolipoic acid} & \quad \text{NAD}^+ \quad \text{NADH} \quad \text{H}^+ \\
\text{SH} & \quad \text{SH} \\
\text{CH}_2 \text{COOH} & \quad \text{CH}_2 \text{COOH}
\end{align*}
\]

NAD\(^+\) (nicotinamide adenine dinucleotide) is a coenzyme found in all living cells. It is involved in key redox reactions in metabolism. NAD\(^+\) is an oxidizing agent and acts by removing a proton and a hydride ion from a substrate. The reduced form, NADH, acts as a reducing agent. The structure of NAD\(^+\) is drawn below.

\[
\begin{align*}
\text{NAD}^+ & \quad \text{NADH} \quad \text{H}^+ \\
\text{R} & \quad \text{R} \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{K} & \quad \text{K}
\end{align*}
\]

(R = adenine dinucleotide)

Draw the structure of NADH.