A. Lidocaine: how does it work?

1. The importance of pH and pKₐ

To understand how lidocaine 1 (Figure 1) works we must begin by making reference to acidity and basicity. It turns out that the pH of the environment in which the drug finds itself is very important.

![Figure 1: The structure of lidocaine.](image)

(1) To begin with write down the equation for pH:

\[ \text{pH} = \]

Thus we can see that the concentration of hydrogen ions, present as H₃O⁺ in water, is of vital importance. If we dissolve an acid in water we will set up the following equilibrium:

\[ \text{HA} + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^+ + \text{A}^- \quad \text{eq. 1} \]

(2) Write down the formula for the equilibrium constant for eq. 1:

\[ K_a = \]

(3) If HA is switched from a weaker acid to a stronger acid to which side will the equilibrium move?

(4) With the stronger acid will \( K_a \) be larger or smaller?
(5) Because the range of values for $K_a$ is very large the position of this equilibrium is usually expressed in logarithmic units as follows:

$$pK_a = -\log K_a \quad \text{eq. 2}$$

(6) As the acid, HA, gets stronger what will happen to the value of $pK_a$?

(7) What is a Brønsted base?

We must now examine how we deal with bases (B) in this scheme for measuring the acidity of compounds. We can write an equilibrium similar to that in eq. 1:

$$\begin{array}{c}
\text{BH}^+ + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^+ + \text{B}^-
\end{array} \quad \text{eq. 3}$$

Acid form \hspace{1cm} Base form

When dealing with drugs, the base will normally be a neutral compound with a lone pair of electrons (most commonly a nitrogen). This contrasts with the more familiar situation of a negatively charged Brønsted base such as HO$^-$ as is found in NaOH. Thus we look at the protonated form of the base i.e. after it has acted as a base. In this form it is charged and an acid (BH$^+$) and will now fit into an overall scheme for measuring the acidity of compounds.

(8) Write down an expression for the equilibrium constant of eq. 3:

$$K_a =$$

Recall eq. 2 for $pK_a$.

(9) As the base gets stronger what happens to the value of $K_a$?

(10) As the base gets stronger what happens to the value of $pK_a$?

Below is a list of the $pK_a$ of a series of acids, some of which may be unfamiliar to you, plot these on a line such as that below. This will give you a feeling as to the relative acidity of various acids or, conversely, their basicity (figure 2).
Figure 2: Acidities (pKa values) of some representative acids.

If you pick an acid along your line e.g. triethylammonium (Et$_3$NH$^+$), then any acid to its left e.g. ethanoic acid will protonate its conjugate base (triethylamine) and triethylammonium, in turn, will protonate any to its right e.g. $^-$OH. This is a useful qualitative rule but in analysing the way a drug moves (pharmacokinetics) we would like to be more precise and know what percentage is protonated. The quantitative approach is to use the Henderson-Hasselbach equation which is given in eq. 4 (you may have seen this equation used to calculate the pH of a buffer solution):

$$pK_a = pH + \log \frac{[\text{acid form}]}{[\text{base form}]} \quad \text{eq. 4}$$
The 'acid form' of a neutral base is its protonated form (BH⁺) whereas the 'base form' is the non-protonated form (B).

Now we can begin to analyse lidocaine 1.

(11) Looking at your plot of the pKₐ of various acids would you expect nitrogen a or nitrogen b to be the more basic i.e. the one that will be protonated first?

(12) The pH of blood is about 7.4, using equation 4 calculate the percentage of lidocaine that is in the protonated form. Now repeat this calculation for pH 2 (stomach) and 8.6 (the pH of the ileum).

The well-known anti-inflammatory ibuprofen (2) has the structure and pKₐ shown in Figure 3.
2. The importance of solubility in different solvents

We are used to the simple idea of solubility e.g. how many grams of a compound will dissolve in a given solvent, say water. As we continue our study of the movement of drugs in the body we must now consider that a drug will meet different environments as it circulates around the body. The blood, for instance, is an aqueous environment whereas the membranes, which form the wall of a cell, are very ‘fatty’ in character. Once again we find ourselves in the territory of equilibria as we must assess the preference of a given molecule to dissolve in aqueous or ‘fatty’ parts of the body. Hansch, whom we have
mentioned before, discovered that the solubility of a compound in 1-octanol nicely equates to its solubility in ‘fatty’ tissues.

(1) Draw the structures of 1-octanol and water and compare and contrast these structures with respect to polarity and hydrogen bonding. Will they mix or form two layers?

Thus if we add a drug to a mixture of the two solvents then we can see that the following equilibrium will exist:

\[
\text{Drug}_{\text{water}} \rightleftharpoons \text{Drug}_{\text{octanol}} \quad \text{eq. 5}
\]

If we measure its concentration in each we can define a partition function \( P \):

\[
\log P = \log \frac{[\text{Drug}]_{\text{oct}}}{[\text{Drug}]_{\text{water}}} \quad \text{eq. 6}
\]

Again we use logarithms to keep the range of values smaller (remember now that each unit now represents a power of ten).

To understand an equation it is often a good idea to substitute in some representative numbers. Let's try a couple of values:

(i) if a drug is 100 times more soluble in octanol than water what is its log \( P \)?
(ii) if a drug is 100 times more soluble in water than octanol what is its log \( P \)?

Therefore positive values favour solubility in a(n) ..................environment.
and negative values favour solubility in a(n)..................... environment.

3. Bringing pH and log \( P \) together

Below are two tables of values of log \( P \) vs. pH for the two compounds we did calculations on to determine their percentage protonation. The first is for ibuprofen and the second is for lidocaine. Plot a graph from this data.

**Ibuprofen:**

<table>
<thead>
<tr>
<th>pH</th>
<th>2</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>logP</td>
<td>4.0</td>
<td>3.8</td>
<td>3.1</td>
<td>2.3</td>
<td>1.3</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
### Lidocaine:

<table>
<thead>
<tr>
<th>pH</th>
<th>3.7</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>logP</td>
<td>-0.5</td>
<td>0.2</td>
<td>0.5</td>
<td>1.4</td>
<td>2.0</td>
<td>2.1</td>
<td>2.1</td>
</tr>
</tbody>
</table>

(i) What happens to the percentage of ibuprofen in the protonated form as we lower pH?
(ii) What happens to the solubility of ibuprofen in aqueous media as we lower the pH?
(iii) What happens to the percentage of lidocaine in the protonated form as we lower the pH?
(iv) Therefore, why is lidocaine administered in an aqueous solution as its HCl salt?

This variation in log P with pH is so important that it is given its own symbol, log D, and the pH at which it is measured is added as a subscript e.g. log D$_{7.4}$. It is this quantity that is measured on a daily basis in the pharmaceutical industry.

Now let's look again at the cell wall diagram and decide how lidocaine manages the trick of crossing the cell membrane and yet binding to the sodium channel in a charged state. Draw on Figure 4 the equilibrium that will allow this to take place.

![Figure 4: Lidocaine crossing a membrane and binding to a sodium channel.](image)

4. Side effects and chirality
An interesting point concerns side effects. There are few drugs with no side effects and it is usually a question of minimising them and making sure that at-risk patients do not use inappropriate drugs. In the case of these local anaesthetics some cardiac side effects can be seen. This results from unwanted binding of the drug to certain potassium channels. Now a more positive log P (around 2.3 is optimal) facilitates entry into the nerve cells we are interested in but also allows the drug to move around the body, away from the site of action, by allowing it to cross the membrane around blood vessels. This is the real world! Is there any hope? There is a clue in stereochemistry and it is a very subtle one. It turns out that there are two very interesting relatives of lidocaine that each has a chiral centre in, ropivacaine 3 and bupivacaine 4 (Figure 5).

![Ropivacaine 3](image)

![Bupivacaine 4](image)

*Figure 5: Structures of ropivacaine and bupivacaine.*

It turns out that which enantiomer of these compounds we use has little to no effect on local anaesthesia but makes a very noticeable difference on the cardiac side effects! Thus, they are sold just as the (S)-enantiomer.

• Draw the correct stereochemistry for the (S)-enantiomer of 3 and 4.

Befitting this remarkable property, the (S)-enantiomer of bupivacaine is sold as chirocaaine in recognition of this chiral effect.

**B. How could we make lidocaine?**

Inspection of the structure of lidocaine suggests that the molecule can be broken down into three components.

![Possible synthetic route to lidocaine](image)

*Figure 6: Possible synthetic route to lidocaine.*

An intriguing question is where the aromatic amine comes from. As nitro groups can be reduced to amines then nitration of an aromatic starting material may offer a hope.
• Look up reaction conditions to transform an aromatic nitro group to an amine.

![Molecule](image)

*Figure 7: Can we nitrate meta-xylene?*

First we need to understand the mechanism of the nitration reaction; surprisingly, what we have learned about $pK_a$ will be very useful to us.

1. When we carry out a nitration reaction we usually use a mixture of sulfuric and nitric acids, using your $pK_a$ scale which will protonate which?

   ![Diagram](image)

   Sulfuric acid Nitric acid

2. The active species in a nitration is $\text{NO}_2^+$ (nitronium ion), can you draw arrows to illustrate how this could form from sulfuric and nitric acids?

   ![Diagram](image)

3. Look up the mechanism of nitration of benzene, then, by drawing curly arrows, complete the diagrams below:
(4) The structure 5 is known as the Wheland intermediate. The positive charge is not localised on one carbon but distributed onto three carbons. Draw arrows to show how the electrons move to interconvert these resonance structures.

(5) An interesting consequence of this is that any electron-releasing group, placed at the positions where the charge resonates to, tends to stabilise the Wheland intermediate. A methyl group is electron releasing. Using this information, if we attempted to nitrate toluene (methylbenzene) which two compounds should be formed predominantly?

(6) If we now return to our compound, meta-xylene, which two nitro-compounds are most likely to form?

(7) The methyl group introduces what we refer to as 'steric bulk' to the ring and incoming nitronium ions try to avoid it. Therefore, of the two, which will favoured?

Yes, here we are in the real world again! We have to suck it up and separate the one we need from the mixture.
Thus, a possible synthetic scheme could be:

\[
\begin{align*}
\text{6} & \quad \xrightarrow{\text{NO}_2} \quad \text{7} \\
\text{10} & \quad \xrightarrow{\text{NaOH}} \quad \text{9} \\
\text{10} & \quad \xrightarrow{\text{HN-CH}_2} \quad \text{11}
\end{align*}
\]

- Which reagent could be used to convert 6 into 7?
- Suggest a reagent to convert 8 into 9.
- Look up and write down the mechanism of amide bond formation from an acid chloride and an amine and hence how to convert 7 into 10.
- What is the class of reaction involved in the conversion of 10 into 11?
- Draw a mechanism for the conversion of 10 into 11. What reagent could the product (11) be treated with to give lidocaine?