

Physical and chemical properties of drug molecules

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Introduction

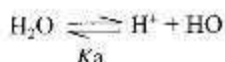
The physical properties of organic molecules such as pKa and partition coefficient are dealt with extensively in pharmacy courses^{1,2} but do not feature greatly in analytical chemistry courses. It is often surprising that analytical chemists cannot distinguish between, for instance, basic, weakly basic, acidic, weakly acidic and neutral nitrogen functions. The physical properties of drug molecules along with simple chemical derivatisation and degradation reactions play an important part in the design of analytical methods. Drug molecules can be complex, containing multiple functional groups that in combination produce the overall properties of the molecule. This chapter will serve as a starting point for understanding the chemical and physico-chemical behaviour of drug molecules that influence the development of analytical methods. The latter part of the chapter focuses on some typical drugs that are representative of a class of drug molecules and lists their physical properties and the properties of their functional groups in so far as they are known.

Calculation of pH value of aqueous solutions of strong and weak acids and bases

Dissociation of water

The pH of a solution is defined as $-\log [H^+]$, where $[H^+]$ is the concentration of hydrogen ions in solution.

In pure water the concentration of hydrogen ions is governed by the equilibrium:



K_a is the dissociation constant for the equilibrium, is known as K_w in the case of the dissociation of water and is determined by the following expression:

$$K_w = \frac{[H^+][HO^-]}{[H_2O]} = [H^+][HO^-] = 10^{-14}$$

Since the concentration of water does not change appreciably as a result of ionisation its concentration can be regarded as not having an effect on the equilibrium and it can be omitted from the equation and this means that in pure water:

$$[H^+] = [HO^-] = 10^{-7}$$

The pH of water is thus given by $-\log 10^{-7} = 7.00$.

Strong acids and bases

If an acid is introduced into an aqueous solution the $[H^+]$ increases.

If the pH of an aqueous solution is known the $[H^+]$ is given by the expression 10^{-pH} , e.g., $[H^+]$ in pH 4 solution $= 10^{-4} \text{ M} = 0.0001 \text{ M}$. Since $[H^+][OH^-] = 10^{-14}$ for water the concentration of $[OH^-]$ in this solution is 10^{-10} M .

A strong acid is completely ionised in water and $[H^+]$ is equal to its molarity, e.g. 0.1 M HCl contains 0.1 M H^+ (10^{-1} M) and has a pH of $-\log 0.1 = 1$. For a solution of a strong base such as 0.1 M NaOH $[OH^-] = 0.1 \text{ M}$ and $[OH^-][H^+] = 10^{-14}$ therefore $[H^+] = 10^{-13} \text{ M}$ and the pH of the solution = 13. Although the pH range is regarded as being between 0–14 it does extend above and below these values, e.g. 10 M HCl in theory has a pH of -1 .

Self-test 2.1

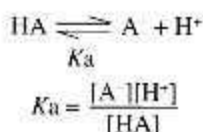
Calculate the pH of the following solutions:

- 0.05 M HCl
- 0.05 M NaOH
- 0.05 M H_2SO_4

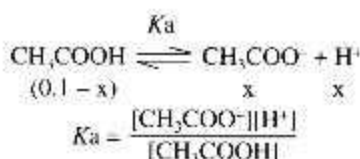
Answers: (i) 1.3; (ii) 12.7; (iii) 1.0 since 0.05 M H_2SO_4 contains 0.1 M H^+

Weak acids and bases

Weak acids are not completely ionised in aqueous solution and are in equilibrium with the undissociated acid, as is the case for water, which is a very weak acid. The dissociation constant K_a is given by the expression below:



For instance in a 0.1 M solution of acetic acid ($K_a = 1.75 \times 10^{-5}$) the equilibrium can be written as follows:



The pH can be calculated as follows:

$$1.75 \times 10^{-5} = \frac{x^2}{(0.1 - x)}$$

Since the dissociation of the acetic acid does not greatly change the concentration of the unionised acid the above expression can be approximated to:

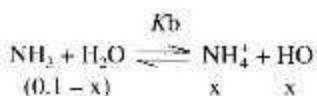
$$1.75 \times 10^{-5} = \frac{x^2}{0.1}$$

$$x = [\text{H}^+] = \sqrt{1.75 \times 10^{-6}} = 0.00132 \text{ M}$$

$$\text{pH} = 2.9$$

In comparison the pH of 0.1 M HCl is 1.

The calculation of the pH of a weak base can be considered in the same way. For instance in a 0.1 M solution of ammonia ($K_b = 1.8 \times 10^{-5}$) the equilibrium can be written as follows:



If the concentration/activity of water is regarded as being 1 then the equilibrium constant is given by the following expression:

$$K_b = \frac{[\text{NH}_4^+][\text{HO}^-]}{[\text{NH}_3]}$$

$$1.8 \times 10^{-5} = \frac{x^2}{(0.1 - x)}$$

The concentration of NH_3 can be regarded as being unchanged by a small amount of ionisation and the expression can be written as:

$$x = [\text{HO}^-] = \sqrt{1.8 \times 10^{-6}} = 0.0013 \text{ M}$$

$$[\text{H}^+] = \frac{K_w}{0.0013} = \frac{10^{-14}}{0.0013} = 7.7 \times 10^{-12} \text{ M}$$

$$\text{pH} = 11.1$$

In comparison the pH of 0.1 M NaOH is 13.

Self-test 2.2

Calculate the pH of the following solutions:

- (i) 0.1 M formic acid ($K_a = 1.77 \times 10^{-4}$)
 (ii) 0.05 M phenol ($K_a = 1.3 \times 10^{-10}$)
 (iii) 0.15 M ethylamine ($K_b = 5.6 \times 10^{-4}$)

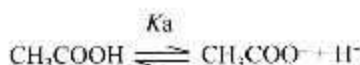
Answers: (i) 2.4 (ii) 5.6 (iii) 11.9

Acidic and basic strength and pKa

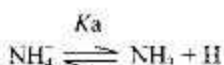
The pKa value of a compound is defined as: $pK_a = -\log K_a$.

A pKa value can be assigned to both acids and bases.

For an acid, the higher the $[H^+]$ the stronger the acid, e.g.:



In the case of a base it is the protonated form of the base that acts as a proton donor, e.g.:



In this case the lower the $[H^+]$ the stronger the base.

If pKa is used as a measure of acidic or basic strength *for an acid, the smaller the pKa value the stronger the acid* for a base *the larger the pKa value the stronger the base*.

Henderson-Hasselbalch equation

$$K_a = \frac{[A^-][H^+]}{[HA]}$$

Can be rearranged substituting pH for $-\log [H^+]$ and pKa for $-\log K_a$ to give:

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

For example when acetic acid (pKa 4.76) is in solution at pH 4.76. The Henderson-Hasselbalch equation can be written as follows:

$$pH = 4.76 + \log \frac{[CH_3COO^-]}{[CH_3COOH]}$$

From this relationship for acetic acid it is possible to determine the degree of ionisation of acetic acid at a given pH.

Thus when the pH = 4.76, then:

$$4.76 = 4.76 + \log \frac{[CH_3COO^-]}{[CH_3COOH]}$$

$$\log \frac{[CH_3COO^-]}{[CH_3COOH]} = 0$$

$$\frac{[CH_3COO^-]}{[CH_3COOH]} = 10^0 = 1$$

Self-test 2.3

Determine the percentage of ionisation of acetic acid at (i) pH 3.76 and (ii) 5.76.

Answers: (i) 50% (ii) 90.6%

Acetic acid is 50% ionised at pH 4.76. In the case of a weak acid it is the protonated form of the acid that is un-ionised and as the pH falls the acid becomes less ionised.

For a base the Henderson-Hasselbalch equation is written as follows:

$$\text{BH}^+ \rightleftharpoons \text{B} + \text{H}^+$$

$$\text{pH} = \text{pK}_a + \log \frac{[\text{B}]}{[\text{BH}^+]}$$

For example when ammonia (pK_a 9.25) is in a solution at pH 9.25 Henderson-Hasselbalch equation can be written as follows:

$$9.25 = 9.25 + \log \frac{[\text{NH}_3]}{[\text{NH}_4^+]}$$

$$\log \frac{[\text{NH}_3]}{[\text{NH}_4^+]} = 0$$

$$\frac{[\text{NH}_3]}{[\text{NH}_4^+]} = 10^0 = 1$$

Ammonia is 50% ionised at pH 9.25. In this case it is the protonated form of the base that is ionised and as the pH falls the base becomes more ionised.

Self-test 2.4

Calculate the percentage of ionisation of ammonia at (i) pH 8.25 and (ii) pH 10.25.

Answers: (i) 90.6% (ii) 60.6%

An alternative way of writing the expression giving the percentage of ionisation for an acid or base of a particular pK_a value at a particular pH value is:

$$\text{Acid: \% ionisation} = \frac{10^{\text{pH} - \text{pK}_a}}{1 + 10^{\text{pH} - \text{pK}_a}} \times 100$$

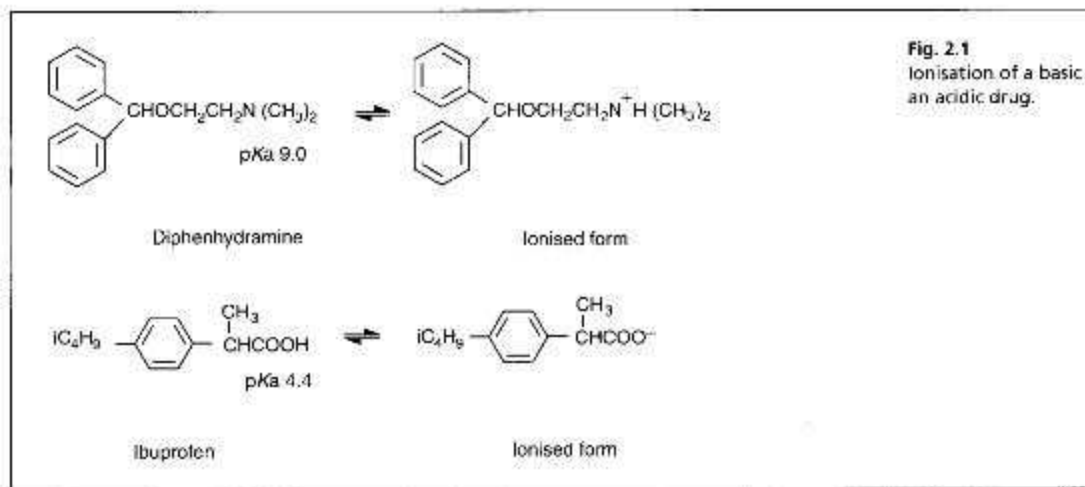
$$\text{Base: \% ionisation} = \frac{10^{\text{pK}_a - \text{pH}}}{1 + 10^{\text{pK}_a - \text{pH}}} \times 100$$

Ionisation of drug molecules

The ionisation of drug molecules is important with regard to their absorption into the circulation and their distribution to different tissues within the body. The pK_a value of a drug is also important with regard to its formulation into a medicine and to the design of analytical methods for its determination.

Calculation example 2.1

Calculate the percentage of ionisation of the drugs shown in Figure 2.1 at pH 7.0

**Diphenhydramine**

This drug contains one basic nitrogen and at pH 7.0 its percentage of ionisation can be calculated as follows:

$$\begin{aligned} \% \text{ Ionisation diphenhydramine} &= \frac{10^{9.0-7.0}}{1 + 10^{9.0-7.0}} \times 100 \\ &= \frac{10^{2.0}}{1 + 10^{2.0}} \times 100 = \frac{100}{101} \times 100 = 99.0\% \end{aligned}$$

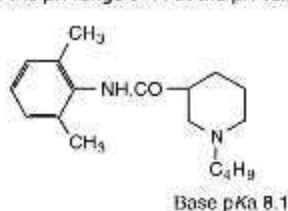
Ibuprofen

This drug contains one acidic group and at pH 7.0 its percentage of ionisation can be calculated as follows:

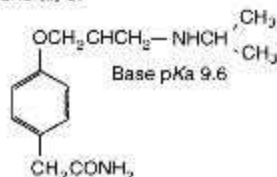
$$\begin{aligned} \text{percentage of ionisation of ibuprofen} &= \frac{10^{7.0-4.4}}{1 + 10^{7.0-4.4}} \times 100 \\ &= \frac{10^{2.6}}{1 + 10^{2.6}} \times 100 = \frac{398}{399} \times 100 = 99.8\% \end{aligned}$$

Self-test 2.5

Calculate the percentage of ionisation of the following drugs, which contain 1 group, which ionises in the pH range 0–14 at the pH values of (i) 4 and (ii) 9.



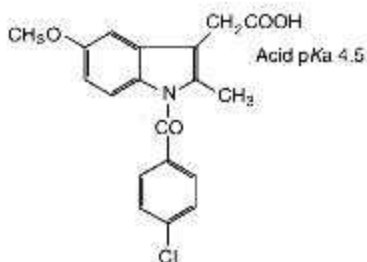
Bupivacaine



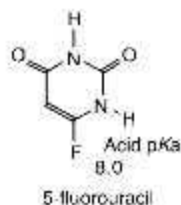
Atenolol

Acidic drugs

Acidic drugs



Indomethacin



5-fluorouracil

Answers: Bupivacaine (i) 99.99%, (ii) 11.2%; Atenolol (i) 99.99%, (ii) 79.9%; Indomethacin (i) 24.0%, (ii) 99.99%; 5-Fluorouracil (i) 0.01%, (ii) 90.9%

Buffers

Buffers are used in a number of areas of analytical chemistry such as the preparation of mobile phases for chromatography and the extraction of drugs from aqueous solution. The simplest type of buffer is composed of a weak acid or base in combination with a strong base or acid. A common buffer system is the sodium acetate/acetic acid buffer system. The most direct way of preparing this buffer is by the addition of sodium hydroxide to a solution of acetic acid until the required pH is reached. The most effective range for a buffer is 1 pH unit either side of the pKa value of the weak acid or base used in the buffer. The pKa value of acetic acid is 4.76 thus its effective buffer range is 3.76–5.76.

Calculation example 2.2

1 litre of 0.1 M sodium acetate buffer with a pH 4.0 is required. Molecular weight of acetic acid = 60 therefore 1 litre of 0.1 M buffer there will be 6 g of acetic acid. To prepare the buffer 6 g of acetic acid are weighed and made up to ca 500 ml with water. The pH of the acetic acid solution is adjusted to 4.0 by addition of 2 M sodium hydroxide solution using a pH meter to monitor the pH. The solution is then made up to 1 litre with water. Calculate the concentration of acetate and acetic acid in the buffer at pH 4.0.

Using the Henderson-Hasselbalch equation:

$$4.00 = 4.76 + \log \frac{[\text{CH}_3\text{COO}^-]}{[\text{CH}_3\text{COOH}]}$$

$$\log \frac{[\text{CH}_3\text{COO}^-]}{[\text{CH}_3\text{COOH}]} = -0.76$$

$$\frac{[\text{CH}_3\text{COO}^-]}{[\text{CH}_3\text{COOH}]} = \frac{10^{-0.76}}{1} = \frac{0.17}{1}$$

The buffer is composed of 1 part acetic acid and 0.17 part acetate.

The buffer was prepared from 0.1 moles of acetic acid, after adjustment to pH 4.0 the amounts of acetic acid and acetate present are as follows:

$$\text{CH}_3\text{COOH} = \frac{1}{1.17} \times 0.1 \text{ moles} = 0.085 \text{ moles}$$

$$\text{CH}_3\text{COO}^- = \frac{0.17}{1.17} \times 0.1 \text{ moles} = 0.015 \text{ moles}$$

Since the acetic acid and acetate are dissolved in 1 litre of water, the buffer is composed of 0.085 M CH_3COOH and 0.015 M CH_3COO^- . Although the concentrations of acetate and acetic acid vary with pH such a buffer can be known as a 0.1 M sodium acetate buffer.

Note: The 0.1 M buffer should not be prepared by adding acetic acid to a solution of 0.1 M NaOH since a large amount of acetic acid would be required to adjust the pH to 4.0; in fact 0.1 moles of NaOH would require 0.57 moles of acetic acid to produce a buffer with pH 4.0 and a strength of 0.57 M.

An alternative way of producing 1 litre of 0.1 M acetate buffer would be to mix 850 ml of a 0.1 M solution of acetic acid with 150 ml of a 0.1 M solution of sodium acetate.

Self-test 2.6

1 litre of a 0.1 ammonium chloride buffer with a pH of 9.0 is required. Ammonia has a pK_a value of 9.25. If a precise molarity is required this buffer is best prepared from ammonium chloride. The pH of the ammonium chloride may be adjusted to pH 9.0 by addition of a solution of sodium hydroxide (assuming the presence of sodium is not a problem). A total of 5.35 g (0.1 moles) of ammonium chloride are weighed and dissolved in ca 500 ml of water. The pH is then adjusted to pH 9.0 by addition of 5M NaOH. The solution is then made up to 1 litre with water.

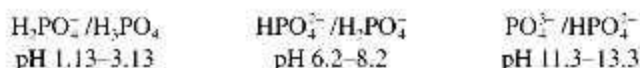
Calculate the concentrations of NH_4^+ and NH_3 in the buffer at pH 9.0 and indicate an alternative method for preparing the buffer.

In this case:

$$\text{pH} = \text{p}K_a + \log \frac{[\text{NH}_3]}{[\text{NH}_4^+]}$$

Answer: 0.036 M NH_3 and 0.064 M NH_4^+ . The buffer could be prepared by mixing 360 ml of a 0.1 M ammonia solution with 640 ml of 0.1 M NH_4Cl .

Some weak acids and bases have more than one buffer range, for example phosphoric acid has three ionisable protons with three different pK_a values and can be used to prepare buffers to cover three different pH ranges. The ionic species involved in the ranges covered by phosphate buffer are:



The buffering ranges of a weak electrolyte are only discrete if the pK_a values of its acidic and/or basic groups are separated by more than 2 pH units. Some acids have ionisable groups with pK_a values less than 2 pH units apart so that they produce buffers with wide ranges. For example, succinic acid, which has pK_a values of 4.19 and 5.57, can be considered to have a continuous buffering range between pH 3.19 and 6.57.

Self-test 2.7

Determine the buffer range(s) for the following compounds:

- (i) Carbonic acid pK_a 6.38, 10.32
- (ii) Boric acid pK_a 9.14, 12.74
- (iii) Glycine 2.34, 9.60
- (iv) Citric acid 3.06, 4.74, 5.4

Answers: (i) 5.38–7.38, 9.32–11.32. The lower range is not useful because of the ease with which CO_2 is lost from solution; (ii) 8.14–10.14, 11.74–13.74; (iii) Glycine: 8.6–10.6; (iv) Citric acid: Continuous buffering range 2.06–6.4

Sometimes a salt of a weak acid with weak base is used in a chromatographic mobile phase to, apparently, set the pH at a defined level, e.g. ammonium acetate or ammonium carbonate. These salts are marginally more effective than a salt of strong acid with a strong base at preventing a change in pH but they are not truly buffers. Such salts have buffering ranges *ca* 1 pH unit either side of the pK_a values of the weak acid and weak base composing them. For example the pH of a solution ammonium acetate is *ca* 7.0 but it does not function effectively as a buffer unless the pH either rises to *ca* 8.25 or falls to *ca* 5.76.

A buffer is most effective where its molarity is greater than the molarity of the acid or base it is buffering against.

Calculation example 12.3

If 10 ml of 0.05 M HCl are added to 100 ml of 0.2 M sodium acetate buffer pH 4.5 the resultant pH can be calculated as follows:

Molarity \times volume = mmoles

Number of mmoles of acetate + acetic acid in 100 ml of buffer = $0.2 \times 100 = 20$ mmoles.

Using the Henderson–Hasselbalch equation:

$$4.5 = 4.76 + \log \frac{[CH_3COO^-]}{[CH_3COOH]}$$

$$\log \frac{[CH_3COO^-]}{[CH_3COOH]} = -0.26$$

$$\frac{[CH_3COO^-]}{[CH_3COOH]} = \frac{10^{-0.26}}{1} = \frac{0.55}{1}$$

The buffer contains 1 part CH_3COOH and 0.55 parts CH_3COO^- :
 $\text{CH}_3\text{COOH} = 1 \times 20 = 12.9$ mmoles $\text{CH}_3\text{COO}^- = \frac{0.55}{1.55} \times 20 = 7.1$ mmoles

When HCl is added the following reaction occurs:



The amount of HCl added is $10 \times 0.05 = 0.5$ mmoles

Therefore after addition of HCl

The amount of acetate remaining is:

$$7.1 - 0.5 = 6.6 \text{ mmoles}$$

The amount of acetic acid now present is:

$$12.9 + 0.5 = 13.4 \text{ mmoles}$$

Therefore the pH of the buffer after addition of HCl is determined as follows (amounts may be substituted in the equation instead of concentrations since CH_3COO^- and CH_3COOH are present in the same volume):

$$\text{pH} = 4.76 - \log \frac{6.6}{13.4} = 4.76 - 0.31 = 4.45$$

The new pH of the buffer is 4.45.

The molarity of the buffer has also changed since the total amount of CH_3COO^- and CH_3COOH is now contained in 110 ml instead of 100 ml giving a new molarity of $0.2 \times \frac{100}{110} = 0.182 \text{ M}$

If 10 ml of 0.05 M HCl were added to 100 ml of water the pH would be determined as follows:

$$-\log \left(0.05 \times \frac{10}{110} \right) = 2.34$$

Self-test 2.8

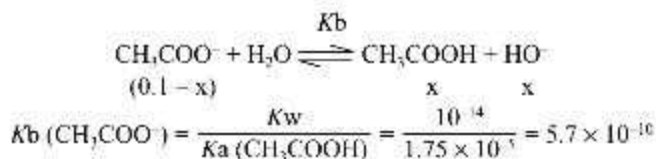
10 ml of 0.1 M HCl are added to 20 ml of a 0.5 M sodium acetate buffer with a pH of 4.3. Calculate: the pH of the buffer after addition of the HCl, the molarity of the buffer after addition of the HCl, the resultant pH if the HCl had been added to 20 ml of water.

Answer: pH = 4.04, new molarity = 0.33, Addition of 10 ml of 0.1 M HCl to 20 ml of water would give a pH of 1.48

Salt hydrolysis

When the salt of a strong acid and a strong base is dissolved in water it produces a pH of ca 7.0. When salts of a weak acid and a strong base or of a strong acid and a weak base are dissolved in water they will produce respectively alkaline and acidic solutions.

When sodium acetate is dissolved in water the acetate ion behaves as a base removing protons from solution. For a weak electrolyte in water $K_b \times K_a = K_w$. If a 0.1 M solution of sodium acetate in water is considered:



Regarding the change in the concentration of water as not affecting the equilibrium and regarding the $[\text{CH}_3\text{COO}^-]$ as being relatively unchanged by hydrolysis.

$$5.7 \times 10^{-10} = \frac{x^2}{0.1}$$

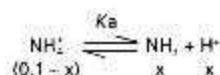
$$[\text{HO}^-] = \sqrt{5.7 \times 10^{-11}} = 7.6 \times 10^{-6}$$

$$[\text{H}^+] = \frac{10^{-14}}{7.6 \times 10^{-6}} = 1.33 \times 10^{-9}$$

$$\text{pH} = 8.9$$

Self-test 2.9

Calculate the pH of a 0.1 M solution of NH_4Cl . Here salt hydrolysis increases $[\text{H}^+]$ and the equilibrium in this case is:



The K_a for this reaction is 5.6×10^{-10} .

Answer: pH = 5.13

Activity, ionic strength and dielectric constant

The activity of ions in a solution is governed by the dielectric constant of the medium they are dissolved in and by the total concentration of ions in solution. For solutions of electrolytes in water with concentrations < 0.5 M the activity of the ions present in solution is usually approximated to their individual concentrations. The mean activity coefficient for an ion in solution is defined as:

$$\gamma_{\pm} = \frac{\text{activity}}{\text{concentration}}$$

Although activity is regarded as 1 in dilute solutions this is still an approximation. The activity of an electrolyte solution in water can be estimated from the following equation:

$$\log \gamma_{\pm} = -0.509 (z_+ z_-) \sqrt{I}$$

$$\text{where } I = \frac{1}{2} \sum m_i z_i^2$$

where -0.509 is a constant related to the dielectric constant of the solvent used to prepare the electrolyte solution and to temperature, z is the charge on a particular ion, I is the ionic strength of the solution and m is the molality (moles per kg of solvent) of a particular ion in solution.

Using this equation the activity of H^+ in 0.1 M HCl can be calculated to be 0.69. Thus the true pH of 0.1 M HCl is calculated as follows:

$$\text{pH} = -\log 0.1 \times 0.69 = 1.2$$

This slight difference between the pH determined from activity and from concentration is usually ignored. However, from the equation used to calculate the activity coefficient it can be seen that the activity decreases with decreasing ionic strength. In addition the constant (-0.509 for water) increases with decreasing

Second extraction

$\frac{5}{6}$ of the 16.7% remaining in the water layer is extracted.

$$\text{Percentage extracted} = \frac{5}{6} \times 16.7 = 13.9\%$$

Percentage of drug remaining in water layer = 2.8%

Third extraction

$\frac{5}{6}$ of the 2.8% remaining in the water layer is extracted.

$$\text{Percentage extracted} = \frac{5}{6} \times 2.8 = 2.3\%$$

Percentage of drug remaining in water layer = 0.5%

Total percentage of drug extracted = 83.3 + 13.9 + 2.3 = 99.5%

Self-test 2.10

A drug has a partition coefficient of 12 between chloroform and water.

Calculate the percentage of a drug that would be extracted from 10 ml of water with (i) 30 ml of chloroform; (ii) 3 × 10 ml of chloroform.

Answers: (i) 99.5% (ii) 99.5%

Effect of pH on partitioning

Many drugs contain ionisable groups and their partition coefficient at a given pH may be difficult to predict if more than one ionised group is involved. However, often one group in a molecule may be much more ionised than another at a particular pH thus governing its partitioning. It is possible to derive from the Henderson–Hasselbalch equation expressions for the variation in the partitioning of organic acids and bases into organic solvent with respect to the pH of the solution that they are dissolved in.

From the Henderson–Hasselbalch equation:

$$\text{For acids: } P_{\text{app}} = \frac{P}{1 + 10^{\text{pH} - \text{pK}_a}}$$

$$\text{For bases: } P_{\text{app}} = \frac{P}{1 + 10^{\text{pK}_a - \text{pH}}}$$

P_{app} is the apparent partition coefficient that varies with pH. Thus it can be seen when a compound, acid or base, is 50% ionised (i.e. $\text{pH} = \text{pK}_a$) its partition coefficient is half that of the drug in the un-ionised state:

$$P_{\text{app}} = \frac{P}{1 + 10^0} = \frac{P}{2}$$

As a general rule for the efficient extraction of a base into an organic medium from an aqueous medium the pK_a of the aqueous medium should be at least 1 pH unit higher than the pK_a value of the base and in the same situation for an acid the pH should be 1 pH unit lower than the pK_a value of the acid.

Calculation example 2.5

A linctus formulation contains the following components:

Base A pKa 6.7, P (chloroform/0.1 M NaOH) = 100	5 mg/ml
Base B pKa 9.7, P (chloroform/0.1 M NaOH) = 10	30 mg/ml
Benzoic acid pKa 4.2 P (chloroform/0.1 M HCl) = 50	5 mg/ml

In order to selectively extract base A 5 ml of the linctus is mixed with 15 ml of phosphate buffer pH 6.7 and extracted once with 60 ml of chloroform.

Calculate the percentage and the weight of each component extracted.

Base A

At pH 6.7:

$$P_{app} = 100/1 + 10^{6.7-6.7} = 100/2 = 50$$

If 20 ml of aqueous buffer phase were extracted with 20 ml of chloroform there would be 1 part of the base in the aqueous phase to 50 parts in the chloroform layer. Since 60 ml of chloroform are used in the extraction there will be 1 part of the base remaining in the aqueous phase and 150 parts in the chloroform layer.

Percentage extracted = $150/151 \times 100 = 99.3\%$

Base A is present at 5 mg/ml in the elixir.

Amount of base A in 5 ml of elixir = $5 \times 5 \text{ mg} = 25 \text{ mg}$

Amount of base A extracted = $25 \times 150/151 = 24.8 \text{ mg}$

Base B

At pH 6.7:

$$P_{app} = 10/1 + 10^{9.7-6.7} = 10/1001 = 0.01$$

If 20 ml of aqueous buffer phase were extracted with 20 ml of chloroform there would be 1 part of the base in the aqueous phase to 0.01 parts in the chloroform layer. Since 60 ml of chloroform are used in the extraction then

1 part of the base will remain in the aqueous phase while there will be 0.03 parts in the chloroform layer.

Percentage extracted = $0.03/1.03 \times 100 = 3.0\%$

Base B is present at 30 mg/ml in the elixir

Amount of base B in 5 ml of elixir = $5 \times 30 \text{ mg} = 150 \text{ mg}$

Amount of base B extracted = $0.03 \times 150 = 4.5 \text{ mg}$

Benzoic acid

At pH 6.7 for an acid:

$$P_{app} = 50/1 + 10^{6.7-4.2} = 50/317 = 0.158$$

If 20 ml of aqueous buffer phase were extracted with 20 ml of chloroform there would be 1 part of the preservative in the aqueous phase to 0.158 parts in the chloroform layer. Since 60 ml of chloroform are used in the extraction

1 part of the benzoic acid will remain in the aqueous phase while there will be 0.474 parts in the chloroform layer.

Percentage extracted = $0.474/1.474 \times 100 = 32.2\%$

Benzoic is present at 5 mg/ml in the elixir

Amount of benzoic acid in 5 ml of elixir = $5 \times 5 \text{ mg} = 25 \text{ mg}$

Amount of benzoic acid extracted = $0.474/1.474 \times 25 = 8.0 \text{ mg}$

The extract is not completely free of the other ingredients in the formulation. If back extraction of the extract with an equal volume of pH 7.7 buffer is carried out approximately 1% of extracted base A will be removed but the amount of base B and benzoic acid will be reduced to < 0.5 mg.

Self-test 2.11

A cough mixture contains the following components:

- | | |
|--|------------|
| (i) Base 1 $pK_a = 9.0$, $P(\text{CHCl}_3/0.1 \text{ M NaOH}) = 1000$ | 30 mg/5 ml |
| (ii) Base 2 $pK_a = 9.7$, $P(\text{CHCl}_3/0.1 \text{ M NaOH}) = 10$ | 30 mg/5 ml |
| (iii) Acidic preservative $pK_a = 4.3$, $P(\text{CHCl}_3/0.1 \text{ M HCl}) = 10$ | 5 mg/5 ml |

5 ml of the cough mixture is mixed with 15 ml of phosphate buffer pH 7.0 and extracted with 60 ml of chloroform. Calculate the weight of each component extracted.

Answers: (i) Base 1 29.0 mg; (ii) Base 2 1.69 mg; (iii) Preservative 0.28 mg

Drug stability

Many drugs are quite stable but functional groups such as esters and lactam rings which occur in some drugs are susceptible to hydrolysis and functional groups such as catechols and phenols are quite readily oxidised. The most common types of degradation which occur in pure and formulated drugs obey zero or first order kinetics.

Zero order degradation

In zero order kinetics the rate of degradation is independent of the concentration of the reactants. Thus if the rate constant for the zero order degradation of a substance is $0.01 \text{ moles h}^{-1}$ then after 10 h 0.1 moles of the substance will have degraded. This type of degradation is typical of hydrolysis of drugs in suspensions or in tablets where the drug is initially in the solid state and gradually dissolves at more or less the same rate as the drug in solution is degraded, i.e. the equilibrium concentration in free solution remains constant.

First order degradation

First order kinetics of drug degradation has been widely studied. This type of degradation would be typical of the hydrolysis of a drug in solution. Such reactions are pseudo first order since the concentration of water is usually in such large excess that it is regarded as constant even though it does participate in the reaction. In first order kinetics the rate constant k has the units h^{-1} or s^{-1} and the rate of the reaction for a drug is governed by the expression:

$$-\frac{d[A]}{dt} = k[A]$$

where A is the concentration of the drug which will change as degradation proceeds. This expression can be written as:

$$\frac{dx}{dt} = k(a-x)$$

which can also be written as

$$\int_0^x \frac{dx}{(a-x)} = \int_0^t k dt$$

where x is the amount of degraded product and a is the starting concentration of the drug. From this expression by integration and rearrangement the following expression arises:

$$t = \frac{1}{k} \ln \frac{a}{a-x}$$

The half-life of the drug (the time taken for 50% of a sample drug to degrade, i.e. where x is $a/2$) is thus given by the following expression:

$$t_{0.5} = \frac{1}{k} \ln \frac{a}{a/2} = \frac{1}{k} \ln 2$$

Thus for aspirin, which has a rate constant of 0.0133 h^{-1} for the hydrolysis of its ester group at 25° and pH 7.0, the half-life can be calculated as follows:

$$t_{0.5} = \frac{0.693}{0.0133} = 52.1 \text{ h}$$

The shelf-life of a drug, the time required for 10% degradation (where x is $0.1 a$), is given by the following expression:

$$t_{0.9} = \frac{1}{k} \ln \frac{a}{0.9a} = \frac{1}{k} \ln 1.11$$

Calculation example 2.6

In a high-pressure liquid chromatography assay of aspirin tablets, 10 extracts are made and the extracts are diluted with mobile phase solution, which consists of acetonitrile/0.1 M sodium acetate buffer pH 4.5 (10:90) and analysed sequentially. If the rate constant for the degradation of aspirin in the mobile phase is 0.0101 h^{-1} at room temperature how long can the analyst store the solutions at room temperature before the degradation of the analyte is greater than 0.5%?

In this case we are interested in $t_{0.995}$: \ln

$$t_{0.995} = \frac{(a/0.995a)}{0.0101} = 0.5 \text{ h}$$

Thus in order for degradation to be < 0.5% the solutions would have to be analysed within 30 min of their being prepared.

Self-test 2.12

Determine the half-lives of the following drugs, which can undergo hydrolysis of their ester functions in solution, under the conditions specified.

- Atropine at 40°C and pH 7.0 where $k = 2.27 \times 10^{-4} \text{ h}^{-1}$.
- Procaine at 37°C and pH 8.0 where $k = 1.04 \times 10^{-2} \text{ h}^{-1}$.
- Benzocaine at 30°C and pH 9.0 where $k = 2.27 \times 10^{-3} \text{ h}^{-1}$.

Answers: (i) 127.2 h; (ii) 66.6 h; (iii) 12.7 h

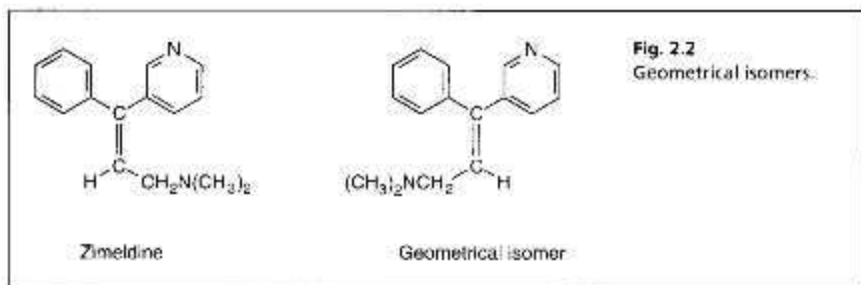
Stereochemistry of drugs

The physiological properties of a drug are governed to a great extent by its stereochemistry. In recent years it has emerged that, in some instances, even optical isomers of a drug can have very different physiological effects. Since

stereochemistry is concerned with the way in which a drug is orientated in space this is something that is difficult to visualise on a flat piece of paper and the assignment of absolute configuration to a drug some people find confusing. The three types of isomerism encountered in drug molecules are geometrical isomerism, optical isomerism and diastereoisomerism.

Geometrical isomerism

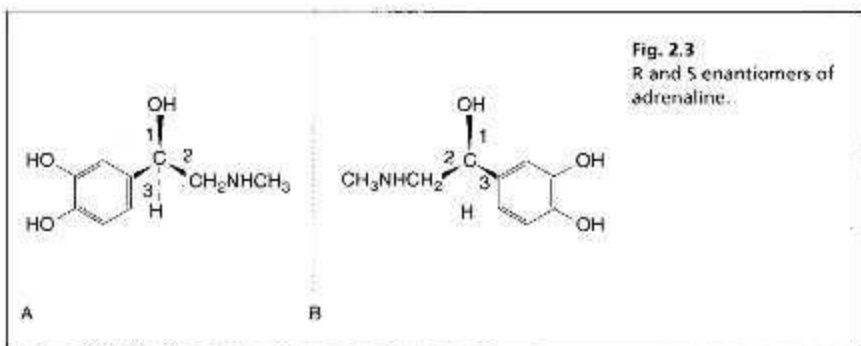
Drugs which have a geometrical isomer are relatively uncommon.



An example of a drug with a geometrical isomer is the antidepressant zimeldine (Fig. 2.2). The lack of free rotation about the double bond ensures that the stereochemistry of this drug and its isomer is different. Zimeldine is the only drug used. Other drugs which could also have geometric isomers of this type include amitriptyline and triprolidine.

Chirality and optical isomerism

Optical isomerism of drug molecules is widespread. Many drug molecules only contain one or two chiral centres. A simple example is the naturally occurring neurotransmitter adrenaline. When a compound has no symmetry about a particular carbon atom the carbon atom is said to be a chiral centre. When a compound contains one or more chiral centres it is able to rotate plane-polarised light to the right (+) or the left (-). A chiral centre arises when a carbon atom has four structurally different groups attached to it.



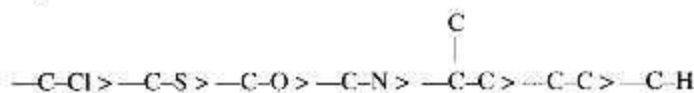
Adrenaline can exist as two enantiomers that are mirror images of each other (Fig. 2.3) and are thus non-superimposable. In Figure 2.3 the wedge-shaped bonds indicate bonds above the plane of the paper, the dotted bonds indicate bonds pointing

down into the paper and unbroken lines indicate bonds in the same plane as the paper. In common with all pairs of enantiomers, the adrenaline enantiomers have identical physical and chemical properties, the only difference in their properties is that the enantiomers rotate plane-polarised light in opposite directions. However, the two enantiomers of adrenaline do have different biological properties, the (-) enantiomer exerts a much stronger effect, for instance, in increasing heart rate. It is not possible simply by looking at a structure drawn on paper to say which way it will rotate plane-polarised light – this can only be determined by experiment. In order to describe the configuration about a chiral centre a set of precedence rules was developed:

- (i) The group of lowest priority attached to the chiral carbon, often hydrogen, is placed behind the plane of the paper with all the other groups pointing forwards.
- (ii) The priorities are assigned to the atoms immediately attached to the chiral centre in order of decreasing atomic mass. For example:



- (iii) If two atoms attached to the chiral centre are of the same precedence the priority is assigned on the basis of the atoms attached to these atoms, for example:

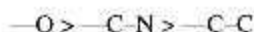


- (iv) If required the third atom in a chain may be considered, for example:



Using these rules we can assign the absolute configurations for adrenaline structures A and B. Placing the group of lowest priority behind the paper, in this case H,

For structure A we find moving in a clockwise direction (clockwise = *R*):



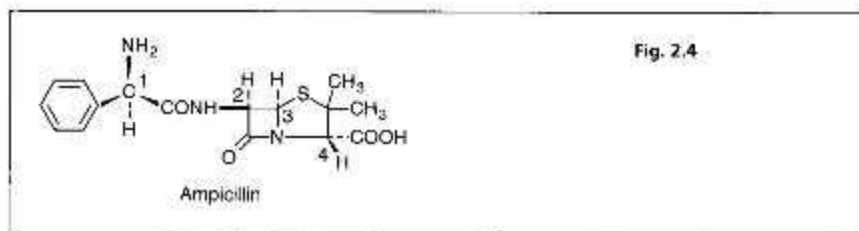
Thus the absolute configuration of A is *R* and it follows that its mirror image B must be *S* (the order of precedence moves anti-clockwise).

To relate the (+) (dextrorotatory) and (-) (laevorotatory) forms of a molecule to an absolute (*R* or *S*) configuration is complex and requires preparation of a crystal of the compound suitable for analysis by X-ray crystallography. In contrast the direction in which a molecule rotates plane-polarised light is easily determined using a polarimeter.

X-ray crystallography of the enantiomers of adrenaline has shown that the (-) form has the *R* configuration and the (+) form has *S* configuration.

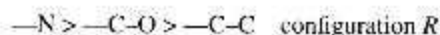
It should be noted that in older literature the terms *d* and *l* are used to denote (+) and (-) respectively and *D* and *L* are used to denote *R* and *S* respectively. A mixture containing equal amounts of (+) and (-) adrenaline or indeed enantiomers of any drug is known as a racemic mixture and of course will not rotate plane-polarised light. The physical separation of enantiomers in a racemic mixture into their pure (+) and (-) forms is often technically difficult.

Ampicillin (Fig. 2.4) provides a more complex example than adrenaline with regard to assignment of absolute configuration since it contains four chiral centres.



Assignment can be made as follows:

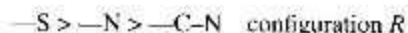
Chiral centre 1:



Chiral centre 2:

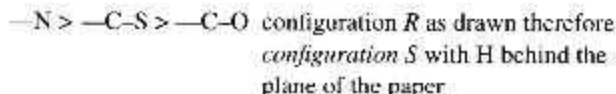


Chiral centre 3:



Chiral centre 4:

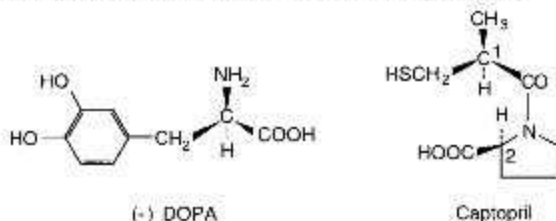
In this case since the molecule is drawn with the hydrogen pointing forward it is best to determine the configuration from the molecule as drawn and then assign the opposite configuration.



The structures of drugs as drawn on paper do not always lend themselves to ready assignment of absolute configuration and sometimes a certain amount of thinking in three dimensions is required in order to draw the structures in a form where the absolute configuration can be assigned. In drugs such as steroids, penicillins and morphine alkaloids, which are all based on natural products, chirality is built into the molecules as a result of the action of the stereoselective enzymes present in the plant or micro-organism producing them. However, there are many synthetic drugs where chiral centres are part of the structure. Many of these drugs are used in the form of racemates since there are technical difficulties in carrying out stereospecific chemical synthesis or in resolving mixtures of enantiomers resulting from non-stereoselective synthesis. In the past many such racemic mixtures have been used as drugs without regard for the fact that effectively a drug that is only 50% pure is being administered. The so called 'inactive' enantiomer may in fact be antagonistic to the active form or it may have different physiological effects.^{3,4} The most notable example, which gave rise to much of the medicines legislation in the past 30 years, is the case of thalidomide, which contains one chiral centre and was administered as a racemate in order to alleviate morning sickness during pregnancy. The active enantiomer produced the intended therapeutic effects whilst the 'inactive' enantiomer was responsible for producing birth defects in the children of mothers who took the racemic drug. Current legislation requires a manufacturer seeking to license a new drug in the form of a racemate to justify the use of the racemate as opposed to a pure enantiomer.

Self-test 2.13

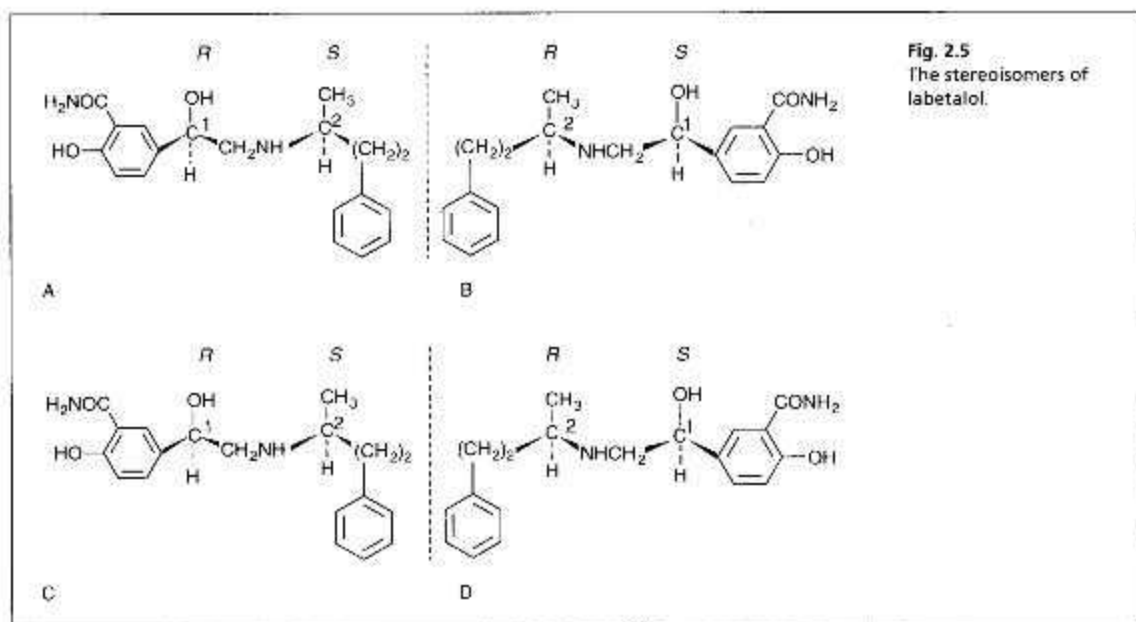
Assign absolute configurations to the chiral centres in the following drugs.



Answers: R (-)-DOPA; captopril 1S,2S

Diastereoisomers

Where more than one chiral centre is present in a molecule there is the possibility of diastereoisomers, e.g. captopril. Another example of a synthetic drug with two chiral centres is labetalol. The number of diastereoisomers arising from n chiral centres is 2^{n-1} , i.e. 2 in the case of labetalol. In the structure shown in Figure 2.5 chiral centres 1 and 2 in structure A have the configurations R and S respectively; the enantiomer of this structure (B) has the S and R configurations in centres 1 and 2. In addition there is a pair of enantiomers C and D that are diastereoisomers of the structures A and B, which have the configurations $1R,2R$ and $1S,2S$.

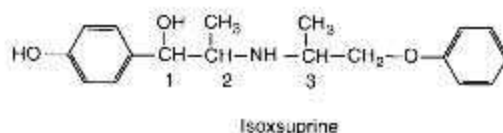


The diastereoisomers in a mixture can be usually separated by ordinary chromatographic methods. In the case of labetalol, two peaks would be seen in a chromatographic trace obtained from a non-chiral phase – one due to the $1R,2S$, $1S,2R$ pair of enantiomers and the other to the $1R,2R$ and $1S,2S$ pair of enantiomers.

The commercial drug is in fact administered as a mixture of all four isomers and the BP monograph for labetalol checks the ratio of the two chromatographic peaks produced by the two enantiomeric pairs of diastereoisomers. In order to separate the enantiomeric pairs a chiral chromatography column would be required and separation on a chiral column produces four peaks (Ch. 12).

Self-test 2.14

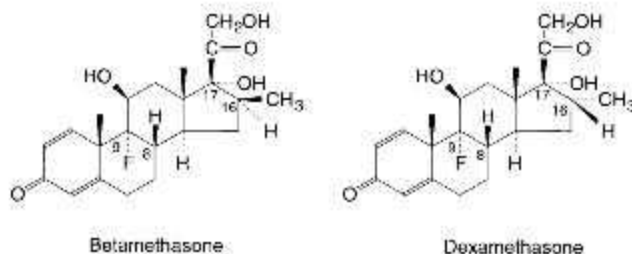
Indicate the configuration of the pairs of enantiomeric diastereoisomers which compose the drug isoxsuprine.



Answer: 1R 2R 3R and 1S 2S 3S; 1R 2R 3S and 1S 2S 3R; 1R 2S 3R and 1S 2S 3R and 1R 2S 3S; 1R 2S 3R and 1S 2S 3R

An example of a pair of diastereoisomers used separately as drugs is betamethasone and dexamethasone shown in Figure 2.6. With a total of eight chiral centres within the betamethasone and dexamethasone structures there is the possibility $2^8 = 64$ isomers of the structure and these divide into 32 enantiomeric pairs. Both dexamethasone and betamethasone could have corresponding enantiomers but because they are largely natural products, made by stereospecific enzymes, their optical isomers do not exist. Semi-synthetic steroids are largely derived via microbial fermentation from naturally occurring plant sterols, originally obtained from the Mexican yam. The partially degraded natural products are then subjected to a number of chemical synthetic steps to produce the required steroid.

Fig. 2.6
An example of diastereoisomers used separately as drug molecules.



In betamethasone and dexamethasone the only stereoisomerism is at the synthetically substituted 16 position. In the case of betamethasone the methyl group is in the β -position, i.e. as one looks down on the molecule, it is closer than the hydrogen at position 16 (not necessarily projecting vertically out of the plane of the paper). In dexamethasone, the methyl group is in the α -position – further away than the hydrogen at 16 (not necessarily projecting vertically down into the paper). Of the two steroids betamethasone has the slightly stronger anti-inflammatory potency. Another stereochemical term is *cis* and *trans* and this refers to the relative orientation of two substituents. In betamethasone the hydroxyl group at 17 and the

methyl group at 16 are trans – on opposite sides of the ring; in dexamethasone the hydroxyl group at 17 and the methyl group at 16 are cis – on the same side of the ring. Otherwise the relative orientation of the substituents is the same in both drugs, e.g. fluorine at 9 and hydrogen at 8 are trans to each other.

Measurement of optical rotation

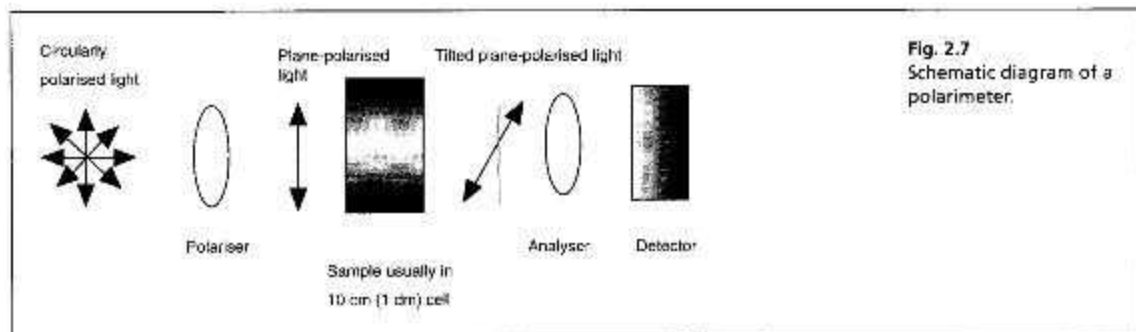


Fig. 2.7
Schematic diagram of a polarimeter.

Figure 2.7 shows a schematic diagram of a polarimeter. Light can be viewed as normally oscillating throughout 360° at 90° to its direction of travel. The light source is usually a sodium lamp, the polarising material can be a crystal of Iceland spar, a Nicol prism or a polymeric material such as polaroid. When circularly polarised light is passed through the polariser its oscillations are confined to one plane. In the absence of an optically active material the instrument is set so that no light is able to pass through the analyser. When the polarised light is passed through an optically active medium the plane in which the light is oscillating in becomes tilted and light is able to pass through the analyser. The angle of rotation can be measured by correcting for the tilt by rotating the analyser until light again does not pass through it. The angle that the second polariser has to be rotated through to, once again, prevent the passage of light through it gives the measured rotation α . The standard value for the rotation produced by an optically active compound is $[\alpha]$ the specific rotation of a substance where:

$$[\alpha] = \frac{100\alpha}{lc}$$

where α is the measured rotation, l is the pathlength of the cell in which the measurement is made in dm and c is the concentration of the sample solution in g/100 ml.

The observed optical rotation is dependent on both the wavelength of the light and the temperature. The sodium D line (589 nm) is usually used to make measurements. The solvent in which the sample is dissolved may also greatly affect the $[\alpha]$ of a substance. Values for $[\alpha]$ are usually quoted with details of the concentration of the solution used for measurement, the solvent, the temperature and the type of light used. For example the specific rotation for (–) adrenaline is given as:

$$[\alpha]^{25}_D = -51^\circ (c = 2, 0.5 \text{ M HCl})$$

The optical rotation was obtained at 25° using the sodium D line with a 2 g 100 ml^{-1} solution in 0.5 M HCl.

If an enantiomer is chemically pure it is possible to determine its degree of enantiomeric purity by measuring its optical rotation relative to a standard value, e.g. if an enantiomeric mixture contains 1% of enantiomer A and 99% of enantiomer B $[\alpha]$ will be reduced by 2% compared to the value for optically pure B. Examples of the measurement of optical rotation as a quality control check are found in the BP monographs for Timolol maleate, Tobramycin and Phenylephrine Hydrochloride.

Self-test 2.15

Optical rotation measurements were made using the sodium D line at 25°C in a 1 dm cell and the readings obtained were as follows:

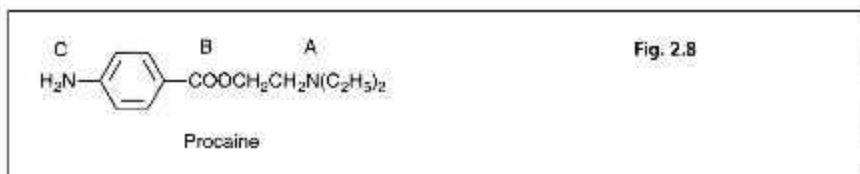
- (i) Phenylephrine HCl 2.6% w/v in 0.1 M HCl; $\alpha = -0.98^\circ$
 (ii) Timolol maleate 9.8% w/v in 1 M HCl; $\alpha = -0.59$

Calculate $[\alpha]$ for these drugs and express it in the conventional form.

(i) $[\alpha]_D^{25} = -37.7^\circ$ (ii) $[\alpha]_D^{25} = -0.60^\circ$ (iii) $[\alpha]_D^{25} = -0.60^\circ$ (iv) $[\alpha]_D^{25} = -0.60^\circ$

Profiles of physico-chemical properties of some drug molecules

Procaine



Drug type: local anaesthetic.

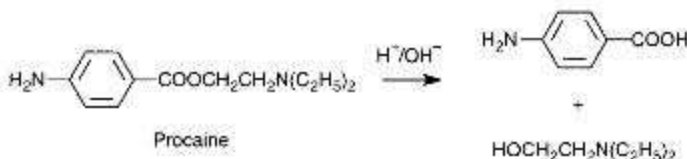
Functional groups:

- A Tertiary aliphatic amine, pK_a 9.0.
- B Ester, neutral.
- C Aromatic amine, very weak base pK_a ca 2.

Half-life in water: 26 d at pH 7.0, 37°C.

Additional information: Procaine is formulated in injections and thus susceptible to aqueous phase hydrolysis, in simple solution its degradation is first order (Fig. 2.9).

Fig. 2.9
Hydrolysis of procaine.



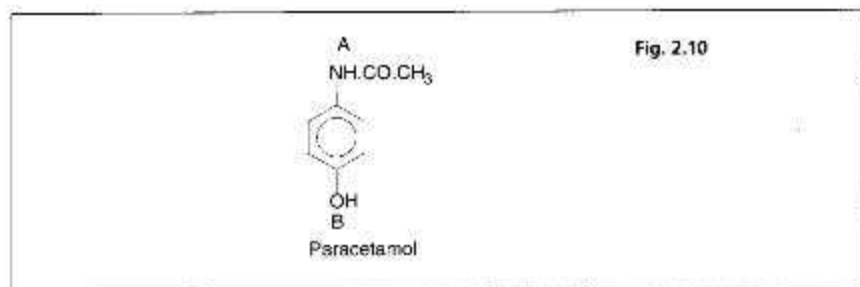
Self-test 2.16

Calculate:

- (i) The percentage ionisation of procaine at pH 7.0 (the ionisation of group C at this pH will be negligible).
 (ii) The rate constant for its hydrolysis at pH 7.0 and 37°C.

Answers: (i) 99.01%; (ii) $1.11 \times 10^{-4} \text{ h}^{-1}$

Closely related drug molecules: Proxymetacaine, benzocaine, amethocaine, butacaine, propoxycaine, procainamide (for stability of an amide group see paracetamol), bupivacaine, lignocaine, prilocaine.

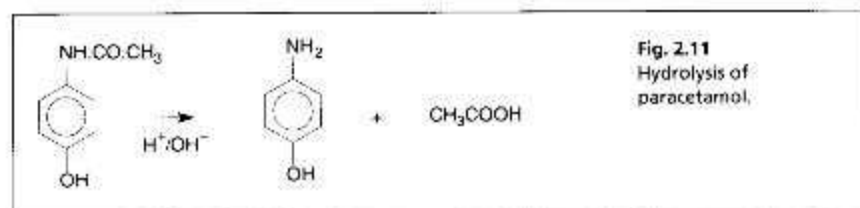
Paracetamol

Drug type: Analgesic.

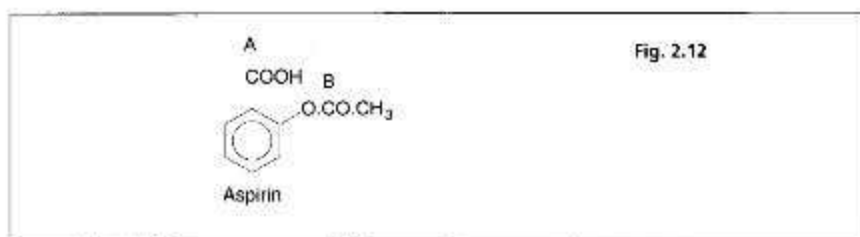
Functional groups:

- A Amide group, neutral.
- B Phenolic hydroxy group very weak acid pK_a 9.5.

Half-life in water: 21.8 years at pH 6 and 25°C. Most amides are very stable to hydrolysis (Fig. 2.11).



Other drugs containing an amide group: Bupivacaine, procainamide, lignocaine, beclamide, acebutolol.



Aspirin

Drug type: Analgesic.

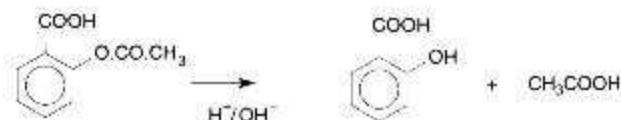
Functional groups:

- A Carboxylic acid, weak acid, pK_a 3.5.
- B Phenolic ester, particularly unstable.

Half-life in water: 52 h at pH 7.0 and 25°C; ca 40 days at pH 2.5 and 25°C.

Additional information: The rate of HO^- catalysed hydrolysis of esters is $>$ the rate of H^+ hydrolysis of esters. Solid aspirin absorbs water from the atmosphere and then hydrolyses (Fig. 2.13).

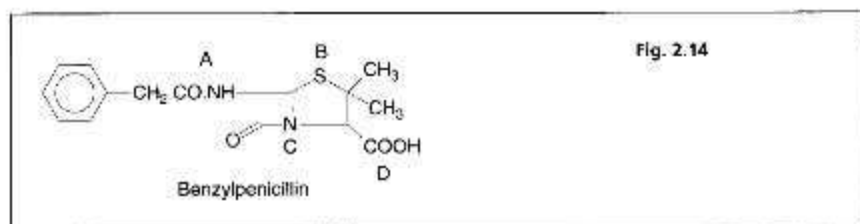
Fig. 2.13
Hydrolysis of aspirin.



Partition coefficient of un-ionised compound at acidic pH: Octanol/water ca 631.

Other drugs containing phenolic ester group: metipranolol, vitamin E, benorylate, dipivefrin.

Benzylpenicillin

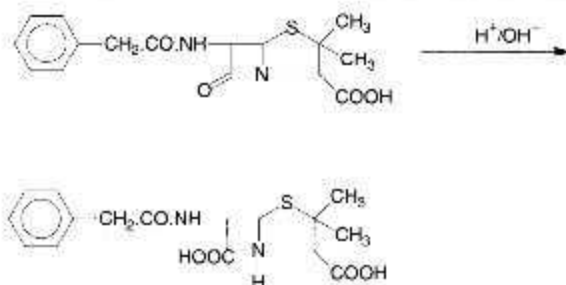


Drug type: antibiotic.

Functional groups:

- A Amide, neutral, relatively stable, see paracetamol.
- B Thioether, neutral, can be oxidised at high levels of oxygen stress.
- C Lactam ring, neutral, particularly susceptible to hydrolysis (Fig. 2.15).

Fig. 2.15
Hydrolysis of
benzylpenicillin.



Half-life: benzylpenicillin: 38 d at pH 6.75 and 30°; ampicillin: 39 d at pH 6.5 and 25°.
Additional information: Consideration of the stability of these compounds is particularly important since they may be formulated as oral suspensions.

- D Carboxylic acid, weak acid pKa 2.8 (the strength of the acid is increased by the adjacent lactam ring).

Compounds with similar properties: amoxicillin, cloxacillin, carbenicillin, flucloxacillin, phenoxymethylpenicillin, cephalixin, cefuroxime.

5-Fluorouracil

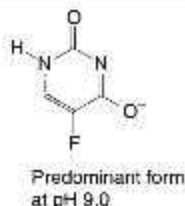
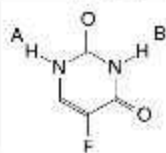


Fig. 2.16
5-Fluorouracil and its
ionised form.

Drug type: anticancer

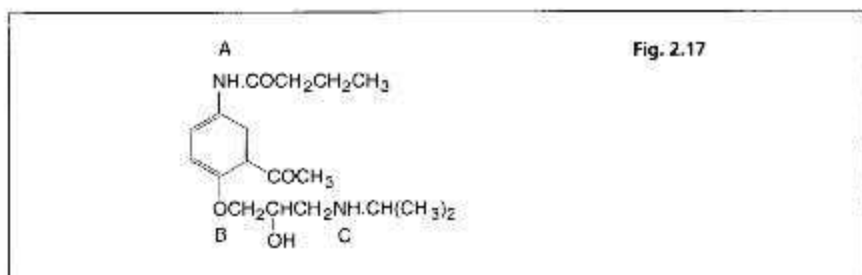
Functional groups:

- A Ureide nitrogen, acidic, pKa 7.0.
- B Ureide nitrogen, very weakly acidic, pKa 13.0.

Additional information: The molecule is quite stable.

Partition coefficient of un-ionised molecule: Octanol/water ca 0.13.

Compounds containing an acidic nitrogen in a heterocyclic ring: phenobarbitone, amylobarbitone, butobarbitone, bemegride, uracil, phenytoin, theophylline, theobromine.



Acebutolol

Drug type: β -adrenergic blocker.

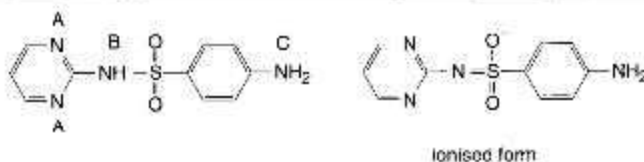
Functional groups:

- A Amide, neutral, susceptible to hydrolysis under strongly acidic conditions (see paracetamol).
- B Aromatic ether group, potentially oxidisable under stress conditions.
- C Secondary amine group pK_a 9.4.

Partition coefficient of un-ionised compound: Octanol/water ca 483.

Sulphadiazine

Fig. 2.18
Sulphadiazine and its ionised form.



Drug type: antibacterial (Fig. 2.18).

Functional groups:

- A Diazine ring nitrogens, very weakly basic pK_a < 2.
- B Sulphonamide nitrogen, weak acid, pK_a 6.5.
- C Weakly basic aromatic amine pK_a < 2.

Partition coefficient of un-ionised compound: Octanol/water ca 0.55 (log P octanol/water at pH 7.5 = -1.3).

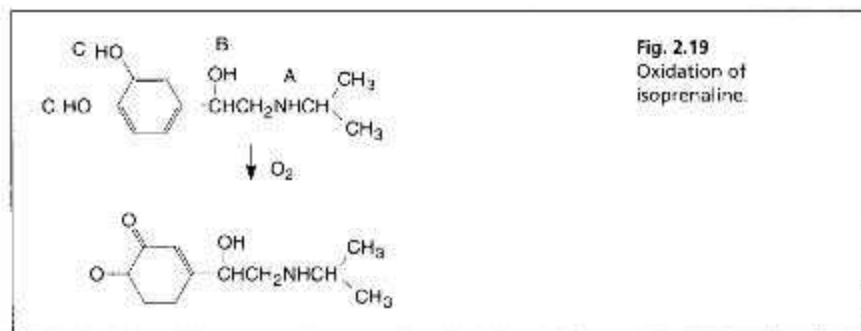
Closely related compounds: sulphadoxine, sulphamerazine, sulphamctopyrazine, sulphaquinoxaline, sulphachloropyridazine, sulphamethoxazole, sulphathiazole.

Self-test 2.17

Calculate the % ionisation of sulphadiazine at pH 7.5.

Answer: 90.9%. The weakly basic groups in the molecule are not ionised to any degree at pH 7.5.

Isoprenaline



Drug type: sympathomimetic (Fig. 2.19).

Functional groups:

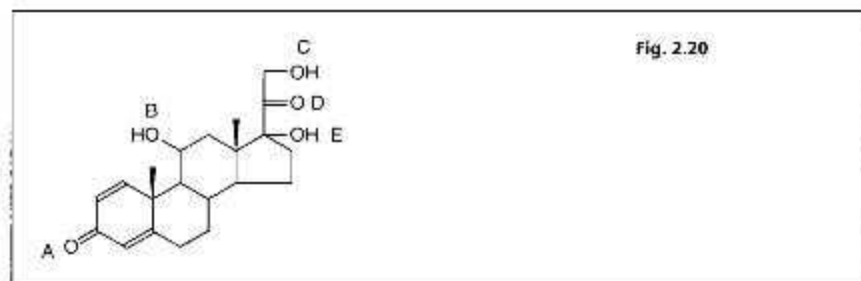
- A Secondary amine, base pKa 8.6.
- B Benzyl alcohol group, neutral.
- C Catechol group, weakly acidic pKa values ca 10 and 12.

Additional information: As indicated in the reaction above, the catechol group is very readily oxidised upon exposure to light or air. Oxidation results in such compounds turning brown, solutions of isoprenaline and related compounds must contain antioxidants as preservatives.

Partition coefficient of the un-ionised drug: The compound is highly water soluble and cannot be extracted to any great extent into an organic solvent since it is ionised to some extent at all pH values.

Closely related compounds: Dopamine, adrenaline, noradrenaline, terbutaline, DOPA.

Prednisolone



Drug type: corticosteroid (Fig. 2.20).

Functional groups:

- A and D ketone groups neutral.
- B and C secondary and primary alcohol groups, neutral.
- E Tertiary alcohol group, neutral, prone to elimination by dehydration at high temperatures. Where the hydroxyl group at E is converted to an ester such as valerate, e.g. betamethasone valerate, thermal elimination of the ester can occur quite readily. Another decomposition reaction of the valerate esters is the

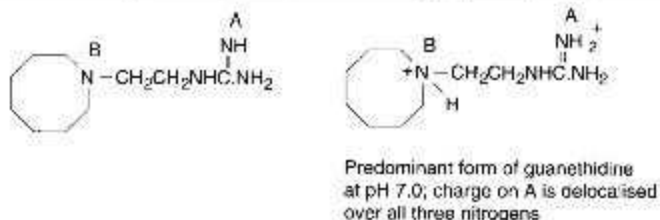
intramolecular transfer of the ester group from E to C (see the BP tests for Betamethasone Valerate products).

Partition coefficient: Octanol/water *ca* 70. The drug does not ionise so that the partition coefficient is unaffected by pH. Despite being neutral compound the hydroxyl groups in prednisolone give it a water solubility of *ca* 0.5 mg/ml.

Closely related compounds: dexamethasone, betamethasone, triamcinolone, hydrocortisone, betamethasone valerate, betamethasone dipropionate.

Guanethidine

Fig. 2.21
Guanethidine and its ionised form.



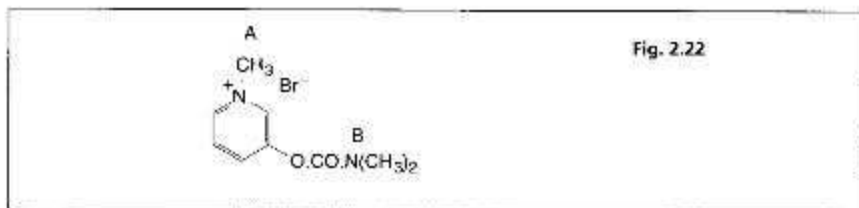
Drug type: anti-hypertensive (Fig. 2.21).

Functional groups:

- A Guanidine group; one of the strongest nitrogen bases pK_a 11.4.
- B Tertiary amine pK_a 8.3.

Compounds containing guanidine group: arginine, creatinine, bethanidine, streptomycin, phenformin, metformin, chlorhexidine.

Pyridostigmine bromide



Drug type: anti-cholinergic.

Functional groups:

- A Salt of strongly basic quaternary ammonium ion. Quaternary ammonium ions are charged at all pH values.
- B Carbamate group, the nitrogen is neutral as in an amide but the carbamate group is less stable than an amide having a stability similar to that of a phenolic ester.

Compounds containing a quaternary ammonium group: atracarium besylate, bretylium tosylate, clindium bromide, glycopyrronium bromide.

Additional problems

1. Calculate the pH of the following solutions assuming that the concentration and the activity of the solutions are the same:

- 0.05 M HCl.
- 0.1 M chloroacetic acid ($K_a = 1.4 \times 10^{-3}$).
- 0.1 M phosphoric acid (First $K_a = 7.5 \times 10^{-3}$).
- 0.1 M fumaric acid ($K_a = 9.3 \times 10^{-4}$ and 3.4×10^{-5}).
- 0.1 M di-isopropylamine base ($K_b = 9.09 \times 10^{-5}$).
- 0.1 M imidazole base ($K_b = 1.6 \times 10^{-7}$).

Answers: (i) 1.0; (ii) 2.8; (iii) 2.1; (iv) 2.9; (v) 10.1; (vi) 11.5.

2. Calculate the pH of the following salt solutions:

- 0.1 M sodium formate (K_a formic acid = 1.77×10^{-4}).
- 0.1 M sodium fusidate (K_a fusidic acid = 4.0×10^{-5}).
- 0.1 M ephedrine hydrochloride (K_a of ephedrine = 2.5×10^{-9}).

Answers: (i) 8.3; (ii) 8.4; (iii) 9.2.

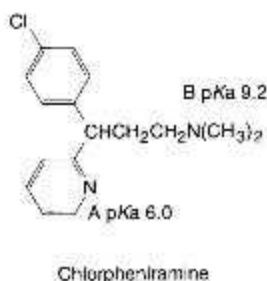
3. Calculate what volumes of the salt solutions specified which would be required to prepare 1 l of the following buffers:

- 0.1 M phosphoric acid/0.1 M sodium dihydrogen phosphate pH 2.5 (pK_a $H_2PO_4^-$, 2.13).
- 0.1 M sodium dihydrogen phosphate/0.1 M disodium hydrogen phosphate pH 8.0 (pK_a $H_2PO_4^-$, 7.21).
- 0.1 M sodium bicarbonate/0.1 M sodium carbonate pH 9.5 (pK_a HCO_3^- , 10.32).

Answers: (i) 299 ml/701 ml; (ii) 139.5 ml/860.5 ml; (iii) 662 ml/338 ml.

4. Indicate the percentage of ionisation of the functional groups specified in the following drugs at pH 7.0 (Fig. 2.23).

Fig. 2.23



Answers: theophylline 1.56% (acidic nitrogen); chlorpheniramine A 9.09% B 99.4%

5. Calculate the percentage of the following compounds that would be extracted under the conditions specified:

- A solution of basic drug pK_a 9.2 in an oral liquid is mixed with a buffer having a pH of 7.2 and is extracted with an equal volume of chloroform (the partition coefficient of the un-ionised base into chloroform is 500).
- an acidic drug with a pK_a 4.2 is extracted from a solution of pH 4.5 with an equal volume of chloroform (the partition coefficient of the un-ionised acid into chloroform is 300).

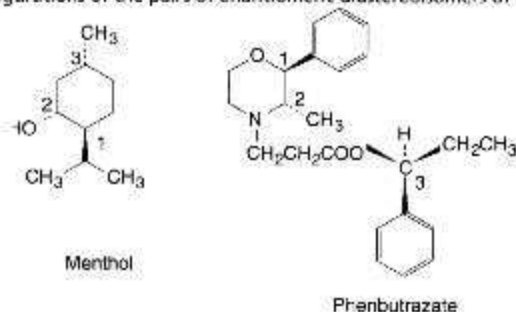
Answers: (i) 99.0%; (ii) 2.8%.

6. Extracts containing benzylpenicillin were prepared for analysis in buffer at pH 6.5 at 25°C, the rate constant for the hydrolysis of benzylpenicillin under these conditions is $1.7 \times 10^{-7} \text{ s}^{-1}$. What is the maximum length of time the solutions can be stored before analysis so that no more than 1% decomposition occurs.

Answers: 16.4 h

7. Determine the absolute configurations of the chiral centres in menthol and phenbutrazate. List the configurations of the pairs of enantiomeric diastereoisomers of menthol (Fig. 2.24).

Fig. 2.24



Answers: Menthol 1S 2R 3R; Phenbutrazate 1S 2S 3S
 Menthol: 1S 2R 3R/1R 2S 2S; 1S 2S 3R/1R 2R 3S; 1S 2S 3S/1R 2R 3R; 1S 2R 3S/1R 2S 3R;
 Phenbutrazate as for menthol.

References

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