2

Alkali Metals

Members of group 1 of the periodic table (first vertical column) with exception of hydrogen are called *alkali metals*. Under the term *alkali metals*, the following elements are included: lithium (Li), sodium (Na), potassium (K), rubidium (Rb), caesium (Cs) and francium (Fr). Generally, francium is not included in further discussions, as only artificial isotopes are known with ^{223}Fr having the longest half-life $T_{1/2} = 21.8$ min (Figure 2.1) [1].

In terms of a clinical use, sodium and potassium are essential ions for the human body and any imbalance in them has to be corrected. Lithium is medically used to treat bipolar disorder (BD), and the application of lithium salts is further discussed within this chapter.

2.1 Alkali metal ions

This group of elements belongs to the so-called s-block metals as they only have one electron in their outer shell, which is of s type. The chemistry of the metals is characterised by the loss of this s electron to form a monocationic ion M^+, which results from the relatively low ionisation energy of this electron (Table 2.1).

*The term **ionisation energy** (IE) is defined as the energy that is required to remove the outer electron of an atom or molecule. The tendency to lose the outer electron is directly correlated to the ionisation energy – the lower the ionisation energy, the easier the removal of the electron.*

Within the group of alkali metals, the ionisation energy for the removal of the outer electron decreases as a result of the increasing distance of this electron from the nucleus.

The loss of the outer s electron within the group of alkali metals results in the formation of the M^+ ion as mentioned. Consequently, most of the compounds of group 1 elements tend to be ionic in nature and form salts. In all pharmaceutical applications, only the salts of alkali metals are used, as most of the pure metals react violently with water.

Essentials of Inorganic Chemistry: For Students of Pharmacy, Pharmaceutical Sciences and Medicinal Chemistry,
First Edition. Katja A. Strohfeldt.

Companion website: www.wiley.com/go/strohfeldt/essentials

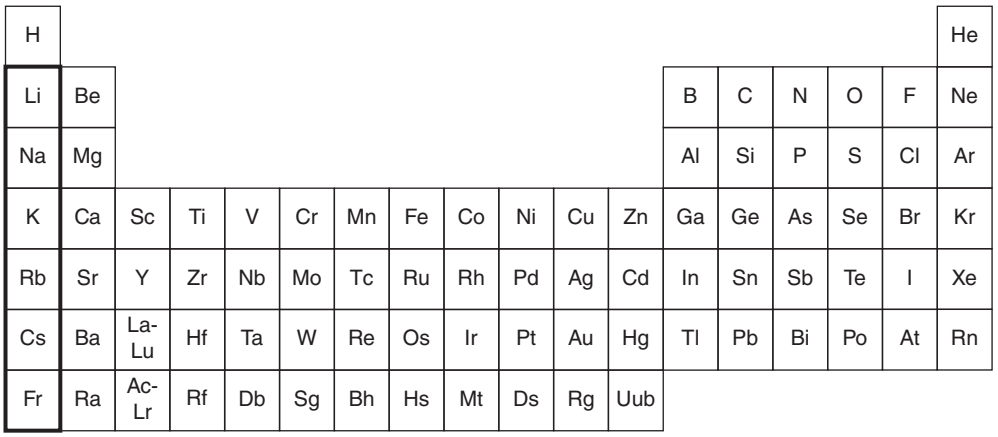

Figure 2.1 *Periodic table of elements; group 1 metals are highlighted*

Table 2.1 *First and second ionisation energies (kJ/mol) for group 1 metals*

	First	Second
Li	520	7296
Na	496	4563
K	419	3069
Rb	403	2650
Cs	367	2420

Source: J. D. Lee, *Concise inorganic chemistry*, 5th ed., Chapman & Hall, London, **1996**.

2.1.1 Extraction of alkali metals: an introduction to redox chemistry

The main sources for Na and K are rock salts. Both elements do not naturally occur in their elemental state. In contrast, Li, Rb and Cs have small natural abundances, but also occur as rock salts. As previously mentioned, only artificial isotopes of Fr are known.

Sodium is manufactured by the so-called Downs' process, which is the electrolysis of molten NaCl and represents the major production process for sodium metal and is also a minor source of industrial chlorine. The process is based on a redox reaction (see Section 2.1.2) where the reduction of liquid Na^+ to liquid Na takes place at the cathode and the oxidation of liquid chloride (Cl^-) to chlorine (Cl_2) gas at the anode:

$$\text{Reduction at the cathode} : \quad Na^+_{(l)} + e^- \rightarrow Na_{(l)}$$

$$\text{Oxidation at the anode} : \quad 2Cl^-_{(l)} \rightarrow Cl_{2(g)} + 2e^-$$

$$\text{Overall redox reaction} : \quad 2Na^+_{(l)} + 2Cl^-_{(l)} \rightarrow 2Na_{(l)} + Cl_{2(g)}$$

Molten NaCl is used as the electrolyte medium within the electrolytic Downs' process and $CaCl_2$ is added in order to decrease the operating temperature. The melting point of NaCl is 800 °C, whereas the addition of $CaCl_2$ lowers it to around 600 °C. The design of the electrolysis cell is crucial in order to prevent oxidation and hydrolysis of freshly produced sodium and recombination to NaCl. Chlorine (Cl_2) is produced at the

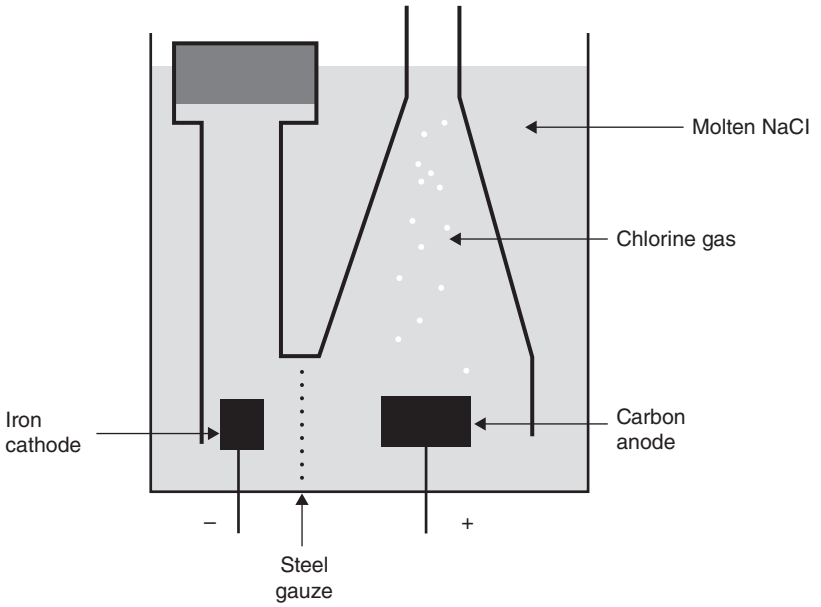

Figure 2.2 *Schematic diagram of Down's cell*

positive graphite anode and captured in form of gas, whereas Na^+ is reduced to liquid sodium at the negative iron cathode and collected in its liquid form.

The anode is defined as the electrode at which the oxidation takes place, which, means in this example, that the anode is positively charged. Conversely, the cathode is defined as the place where the reduction takes place and therefore it is negatively charged in electrolysis processes. Note that the same definition for electrodes applies in a galvanic cell (e.g. in batteries), but as a result of the electron flow the anode has a negative charge whereas the cathode is positively charged (Figure 2.2).

Lithium can be isolated in a similar electrolytic process using lithium chloride (LiCl). Spodumene ($LiAlSi_2O_6$) is the main source for LiCl, which is reacted to LiOH by heating with CaO and subsequent conversion to LiCl prior to the electrolysis. Potassium can also be obtained via electrolysis of KCl, but there are more efficient methods, for example, the reaction to a Na-K alloy which can be subsequently distilled.

2.1.2 Excursus: reduction–oxidation reactions

The term redox (short for reduction–oxidation) reaction describes all chemical reactions in which atoms change their oxidation number. Redox reactions have many applications, which can range from industrial processes (see Downs' process) to biological systems, for example, oxidation of glucose in the human body.

A redox reaction contains the two 'half-reactions', namely reduction and oxidation, which are always one set; this means that there is never a reduction reaction without an oxidation.

> ***Redox reactions*** *are a family of reactions that consist of oxidation and reduction reactions. These are always a matched set, that is, there is no oxidation reaction without a reduction reaction. They are called half-reactions, as two half-reactions are needed to form a redox reaction. Oxidation describes the loss of electrons (e^-), whereas the term reduction is used for the gain of electrons (e^-).*

- *Reduction*: Describes the *gain* of electrons or the *decrease* in the oxidation state of an atom or molecule.
- *Oxidation*: Describes the *loss* of electrons or the *increase* in the oxidation state of an atom or molecule.

$$\begin{aligned} \text{Reduction}: \quad & \mathrm{Fe} \rightarrow \mathrm{Fe^{2+}} + 2\mathrm{e^-} \\ \text{Oxidation}: \quad & \underline{\mathrm{Cu^{2+}} \rightarrow \mathrm{Cu} + 2\mathrm{e^-}} \\ \text{Overall redox reaction}: \quad & \mathrm{Fe} + \mathrm{Cu^{2+}} \rightarrow \mathrm{Fe^{2+}} + \mathrm{Cu} \end{aligned} \tag{2.1}$$

Equation 2.1 gives an example for a simple redox reaction.

The terms *oxidant* and *reductant* are important terms used when discussing redox equations. An oxidant is defined as the atom or molecule that oxidises another compound and in turn is reduced itself. Reductants are molecules or atoms that reduce other compounds and as a result are oxidised themselves. Within a redox equation, there is always the oxidant–reductant pair present.

$$\begin{aligned} \text{Reduction}: \quad & \textbf{Oxidant} + \mathrm{e^-} \rightarrow \text{Product} \\ & \text{Decrease in oxidation state (gain of electrons)} \\ \text{Oxidation}: \quad & \textbf{Reductant} \rightarrow \text{Product} + \mathrm{e^-} \\ & \text{Increase in oxidation state (loss of electrons)} \end{aligned} \tag{2.2}$$

Equation 2.2 shows the involvement of an oxidant and a reductant in redox reactions.

2.1.2.1 The oxidation state

It is actually not precisely correct to describe oxidation/reduction reactions as loss/gain of electrons. Both reactions are better referred to the changes in oxidation state rather than to the actual transfer of electrons; there are reactions classified as redox reaction even though no transfer of electrons takes place.

*The **oxidation state** of an atom describes how many electrons it has lost whilst interacting with another atom compared to its original state (in its elemental form). The oxidation state is a hypothetical charge that an atom would have if all bonds within the molecule are seen as 100% ionic. When a bond is formed, it is possible for an atom to gain or lose electrons depending on its electronegativity. If an atom is electropositive, it is more likely to take electrons away from another atom, and vice versa.*

The oxidation number relates to the number of electrons that has been allocated to each atom; that is, if an atom has gained an electron, its oxidation state is reduced by 1 and therefore this atom has the oxidation state of –I.

IUPAC has defined the oxidation state as follows: A measure of the degree of oxidation of an atom in a substance. It is defined as the charge an atom might be imagined to have when electrons are counted according to an agreed-upon set of rules:

1. The oxidation state of a free element (uncombined element) is zero.
2. For a simple (monatomic) ion, the oxidation state is equal to the net charge on the ion.
3. Hydrogen has an oxidation state of 1 and oxygen has an oxidation state of -2 when they are present in most compounds (exceptions to this are that hydrogen has an oxidation state of -1 in hydrides of active metals, e.g. LiH, and oxygen has an oxidation state of -1 in peroxides, e.g. H_2O_2).

+I –II	+III –II
H_2O	NO_2^-
+I +VII –II	+I +IV –II
$KMnO_4$	H_2SO_3
+VI –II	–IV +I
$Cr_2O_7^{2-}$	CH_4
+III –II	+V –II
Fe_2O_3	BrO_3^-

Figure 2.3 *Example of oxidation states*

4. The algebraic sum of the oxidation states of all atoms in a neutral molecule must be zero, whilst in ions the algebraic sum of the oxidation states of the constituent atoms must be equal to the charge on the ion. For example, the oxidation states of sulfur in H_2S, S_8 (elementary sulfur), SO_2, SO_3 and H_2SO_4 are, respectively: −2, 0, +4, +6 and +6. 'The higher the oxidation state of a given atom, the greater its degree of oxidation; the lower the oxidation state, the greater its degree of reduction (Figure 2.3)' [2].

2.1.2.2 How to establish a redox equation?

In order to describe the overall redox reaction, the establishing and balancing of the half-reaction is essential. In aqueous reactions, generally electrons, H^+, OH^- and H_2O can be used to compensate for changes, whereas it has to be kept in mind whether the reaction takes place under acidic or basic conditions. There are five steps to follow in order to successfully establish a redox equation:

Example

Determine the redox equation for the reaction of MnO_4^- to Mn^{2+} and Ag to Ag^+ under acidic conditions.

1. Determine the oxidation state of each element involved (oxidation number is stated in Roman numbers):

$$\begin{array}{rcl} \text{+VII} \ \text{–II} & & \text{+II} \\ MnO_4^- & \rightarrow & Mn^{2+} \\ \\ 0 & & \text{+I} \\ Ag & \rightarrow & Ag^+ \end{array}$$

2. Add electrons to the equation; the number of electrons must reflect the changes in the oxidation state:

$$\begin{array}{rcl} \text{+VII} \ \text{–II} & & \text{II} \\ MnO_4^- + 5e^- & \rightarrow & Mn^{2+} \\ \\ 0 & & \text{+I} \\ Ag & \rightarrow & Ag^+ + e^- \end{array}$$

3. Determine which reaction is oxidation or reduction:

$$\begin{array}{rcl} & +\text{VII}\ -\text{II} & \text{II} \\ \text{Red.}: & \text{MnO}_4^- + 5\text{e}^- & \rightarrow \quad \text{Mn}^{2+} \end{array}$$

$$\begin{array}{rcl} & 0 & +\text{I} \\ \text{Ox.}: & \text{Ag} & \rightarrow \quad \text{Ag}^+ + \text{e}^- \end{array}$$

4. Balance reduction and oxidation reaction by using either H^+/H_2O (acidic conditions) or OH^-/H_2O (basic conditions), depending on the reaction conditions, which can be acidic or basic (in this example: acidic conditions):

$$\begin{array}{rcl} & +\text{VII}\ -\text{II} & \text{II} \\ \text{Red.}: & \text{MnO}_4^- + 5\text{e}^- + 8\text{H}^+ & \rightarrow \quad \text{Mn}^{2+} + 4\text{H}_2\text{O} \end{array}$$

$$\begin{array}{rcl} & 0 & +\text{I} \\ \text{Ox.}: & \text{Ag} & \rightarrow \quad \text{Ag}^+ + \text{e}^- \end{array}$$

5. Formulate the redox equation keeping in mind that the number of electrons has to be equal in the reduction and oxidation reactions. If necessary, the oxidation reaction has to be multiplied by the number of electrons in the reduction step, or vice versa.

$$\begin{array}{rcll} & +\text{VII}\ -\text{II} & & \text{II} \\ \text{Red.}: & \text{MnO}_4^- + 5\text{e}^- + 8\text{H}^+ & \rightarrow & \text{Mn}^{2+} + 4\text{H}_2\text{O} \quad / * 1 \end{array}$$

$$\begin{array}{rcll} & 0 & & +\text{I} \\ \text{Ox.}: & \text{Ag} & \rightarrow & \text{Ag}^+ + \text{e}^- \quad / * 5 \\ \hline \text{Redox}: & \text{MnO}_4^- + 5\text{Ag} + 8\text{H}^+ & \rightarrow & \text{Mn}^{2+} + 5\text{Ag}^+ + 4\text{H}_2\text{O} \end{array}$$

Within the above example, the reaction conditions are stated as being acidic. A similar example using basic conditions is stated below and hydroxyl ions and water (OH^-/H_2O) are used in order to balance the half-reactions.

Example

Determine the redox equation for the reaction of MnO_4^- to MnO_2 and Fe^{2+} to Fe^{3+} under basic conditions.

1. Determine the oxidation state of each element involved:

$$\begin{array}{rcl} +\text{VII}\ -\text{II} & & +\text{IV} \\ \text{MnO}_4^- & \rightarrow & \text{MnO}_2 \end{array}$$

$$\begin{array}{rcl} -\text{I} & & +\text{V} \\ \text{Br}^- & \rightarrow & \text{BrO}_3^- \end{array}$$

2. Add electrons to the equation; the number of electrons must reflect the changes in the oxidation state:

$$\begin{array}{rcl} +\text{VII}\ -\text{II} & & +\text{IV} \\ \text{MnO}_4^- + 3\text{e}^- & \rightarrow & \text{MnO}_2 \end{array}$$

$$\begin{array}{rcl} -\text{I} & & +\text{V} \\ \text{Br}^- & \rightarrow & \text{BrO}_3^- + 6\text{e}^- \end{array}$$

3. Determine the redox and the oxidation reaction:

$$\begin{array}{rcl} \text{VII}\ -\text{II} & & +\text{IV} \\ \text{Red.}: \text{MnO}_4^- + 3\text{e}^- & \rightarrow & \text{MnO}_2 \end{array}$$

$$\begin{array}{rcl} -\text{I} & & +\text{V} \\ \text{Ox.}: \text{Br}^- & \rightarrow & \text{BrO}_3^- + 6\text{e}^- \end{array}$$

4. Balance reduction and oxidation reaction by using $\text{OH}^-/\text{H}_2\text{O}$:

$$\begin{array}{rcl} \text{VII}\ -\text{II} & & +\text{IV} \\ \text{Red.}: \text{MnO}_4^- + 3\text{e}^- + 2\text{H}_2\text{O} & \rightarrow & \text{MnO}_2 + 4\text{OH}^- \end{array}$$

$$\begin{array}{rcl} -\text{I} & & +\text{V} \\ \text{Ox.}: \text{Br}^- + 6\text{OH}^- & \rightarrow & \text{BrO}_3^- + 6\text{e}^- + 3\text{H}_2\text{O} \end{array}$$

5. Formulate the redox equation:

$$\begin{array}{rcl} +\text{VII}\ -\text{II} & & +\text{IV} \\ \text{Red.}: \text{MnO}_4^- + 3\text{e}^- + 2\text{H}_2\text{O} & \rightarrow & \text{MnO}_2 + 4\text{OH}^- \ / * 2 \\ -\text{I} & & +\text{V} \\ \text{Ox.}: \text{Br}^- + 6\text{OH}^- & \rightarrow & \text{BrO}_3^- + 6\text{e}^- + 3\text{H}_2\text{O} \ / * 1 \\ \hline \text{Redox}: 2\text{MnO}_4^- + \text{Br}^- + \text{H}_2\text{O} & \rightarrow & 2\text{MnO}_2 + \text{BrO}_3^- + 2\text{OH}^- \end{array}$$

2.1.2.3 How to calculate the redox potential

The spontaneous reaction of $\text{Zn}_{(s)}$ metal with $\text{Cu}^{2+}{}_{(aq)}$ from a Cu(II) solution is the prime example for a redox reaction.

$$\text{Zn}_{(s)} + \text{Cu}^{2+}{}_{(aq)} \rightarrow \text{Zn}^{2+}{}_{(aq)} + \text{Cu}_{(s)}$$

In order to calculate the overall redox potential, it is important to formulate the individual half-equations as reductions first. The standard reduction potential E^0_{red} for each reaction can be taken from standard tables:

$$\text{Cu}^{2+}{}_{(aq)} + 2\text{e}^- \rightarrow \text{Cu}_{(s)} \quad E^0_{red} = +0.340\,\text{V}$$

$$\text{Zn}^{2+}{}_{(aq)} + 2\text{e}^- \rightarrow \text{Zn}_{(s)} \quad E^0_{red} = -0.763\,\text{V}$$

The half-equation with the more positive value is the reduction, whilst the other reaction is the oxidation. In this example, Cu^{2+} will be reduced to Cu whilst $Zn_{(s)}$ metal will be oxidised to Zn^{2+}. The standard potential E^0 of an oxidation half-equation is the negative value of E^0_{red}.

$$\text{Reduction}: \ Cu^{2+}{}_{(aq)} + 2e^- \rightarrow Cu_{(s)} \quad E^0_{red} = +0.340\,V$$

$$\text{Oxidation}: \ Zn_{(s)} \rightarrow Zn^{2+}{}_{(aq)} + 2e^- \quad E^0_{ox} = -(-0.763\,V)$$

In order to calculate the voltage produced by an electrochemical cell (E^0_{cell}), the potentials of all half-equations are added up.

$$E^0_{cell} = E^0_{red} + E^0_{ox}$$

$$\text{For the example above}: \ E^0_{cell} = 0.340\,V + [-(-0.763\,V)] = 1.103\,V$$

If you deal with more complicated redox reactions and half-equations have to be multiplied because of the different numbers of electrons in each half-equation, the standard potential E^0 will not be affected by these coefficients. Furthermore, it is important to note that the above calculations can be used only if both reaction partners are present in the same concentration. Concentration can have an effect, and the overall potential is then calculated by using the so-called Nernst equation (see Section 2.4.2).

Table 2.2 *Table of standard reduction potential under acidic conditions at 25 °C [1]*

	E^0 (V)
$Li^+ + e^- \rightarrow Li$	−3.05
$K^+ + e^- \rightarrow K$	−2.93
$Ba^{2+} + 2e^- \rightarrow Ba$	−2.90
$Na^+ + e^- \rightarrow Na$	−2.71
$Mg^{2+} + 2e^- \rightarrow Mg$	−2.37
$Al^{3+} + 3e^- \rightarrow Al$	−1.66
$Mn^{2+} + 2e^- \rightarrow Mn$	−1.18
$Ga^{3+} + 3e^- \rightarrow Ga$	−0.53
$Tl^+ + e^- \rightarrow Tl$	−0.34
$Fe^{2+} + 2e^- \rightarrow Fe$	−0.44
$Cr^{3+} + 3e^- \rightarrow Cr$	−0.74
$Cr^{3+} + e^- \rightarrow Cr^{2+}$	−0.41
$Ni^{2+} + 2e^- \rightarrow Ni$	−0.25
$Cu^{2+} + e^- \rightarrow Cu^+$	+0.15
$Cu^{2+} + 2e^- \rightarrow Cu$	+0.35
$Cu^+ + e^- \rightarrow Cu$	+0.50
$I_2 + 2e^- \rightarrow 2I^-$	+0.54
$Fe^{3+} + e^- \rightarrow Fe^{2+}$	+0.77
$Br_2 + 2e^- \rightarrow 2Br^-$	+1.07
$MnO_2 + 2e^- \rightarrow Mn^{2+}$	+1.23
$Cl_2 + 2e^- \rightarrow 2Cl^-$	+1.36
$MnO_4{}^- + 5e^- \rightarrow Mn^{2+}$	+1.54
$F_2 + 2e^- \rightarrow 2F^-$	+2.65

2.1.3 Chemical behaviour of alkali metals

Most alkali metals have a silvery white appearance with the exception of caesium which is golden yellow. They are all soft metals and typically can be cut with a knife. The softness of the metal increases within the group; caesium is the softest of the alkali metals.

Alkali metals are generally very reactive and oxidise in the air. The reactivity increases within the group, with lithium having the lowest reactivity and caesium the highest. Therefore, all alkali metals except lithium have to be stored in mineral oil. Lithium as an exception is normally stored under inert gas such as argon. Nevertheless, lithium, sodium and potassium can be handled in air for a short time, whereas rubidium and caesium have to be handled in an inert gas atmosphere.

All alkali metals react violently with water with the formation of the metal hydroxide and hydrogen. Again, lithium is the least reactive alkali metal and reacts 'only' quickly with water, whereas potassium, rubidium and caesium are more reactive and react violently with water.

$$2Li_{(s)} + 2H_2O \rightarrow 2LiOH + H_{2(g)} \uparrow \tag{2.3}$$

In terms of their pharmaceutical applications, alkali metals are not directly useable mainly because of their reaction behaviour in aqueous media. Nevertheless, alkali metal halides, some oxides, carbonates, citrates and other salts are of medicinal interest. NaCl and KCl solutions are important as oral rehydration salts, and KCl can also be used to treat potassium depletion.

In general, alkali metal halides can be prepared by the direct combination of the elements, that is, the reaction of an alkali metal with halogens. Alkali metal halides are very soluble in water, which is important for a potential pharmaceutical application, and partly soluble in organic solvents.

$$2M + X_2 \rightarrow 2MX \tag{2.4}$$

Alkali metal oxides can be synthesised by heating alkali metals in an excess of air. Thereby, the oxide, peroxide or superoxide formation can be observed depending on the metal.

$$\begin{aligned} 4Li + O_2 &\rightarrow 2Li_2O \quad \text{oxide formation} \\ 2Na + O_2 &\rightarrow Na_2O_2 \quad \text{peroxide formation} \\ K + O_2 &\rightarrow KO_2 \quad \text{superoxide formation} \end{aligned} \tag{2.5}$$

Alkali metal carbonates and bicarbonates have wide-ranging pharmaceutical applications. Lithium bicarbonate or citrate is used in the treatment of BD, whereas potassium bicarbonate or citrate is used in over-the-counter drugs as active pharmaceutical ingredients (APIs) against urinary-tract infections (increasing the pH of the urine) in the United Kingdom. Their solubility is highly dependent on the metal and varies from sparingly soluble (e.g. Li_2CO_3) whereas others are very soluble (Figure 2.4).

Sodium carbonate is produced by the so-called Solvay process – one of the most important industrial processes, which was developed in the 1860s by Ernest Solvay. Na_2CO_3 has extensive uses ranging from glass production to its application as a water softener. The starting materials, which are NaCl and $CaCO_3$ (lime stone), are inexpensive and easily available.

$$2NaCl + CaCO_3 \rightarrow Na_2CO_3 + CaCl_2 \tag{2.6}$$

$CaCO_3$ is heated to around 1000 °C, when it is converted to CO_2 and CaO (quicklime).

$$CaCO_3 \rightarrow CO_2 + CaO \tag{2.7}$$

CO_2 is then passed through an aqueous solution of NaCl and NH_3 (ammonia). NH_3 buffers the solution at a basic pH and $NaHCO_3$ (sodium bicarbonate) precipitates out of this solution. $NaHCO_3$ is less water soluble

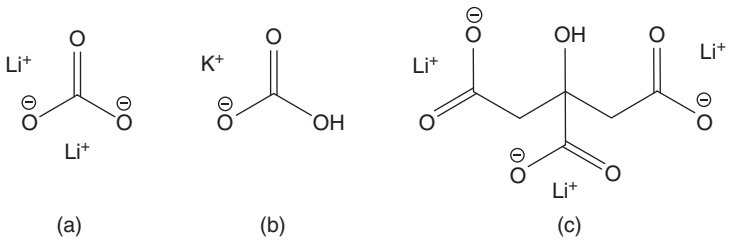

Figure 2.4 *Chemical structures of (a) lithium carbonate, (b) potassium bicarbonate and (c) lithium citrate*

than NaCl at a basic pH. Without the addition of NH_3, the solution would be acidic, as HCl is produced as a by-product.

$$NaCl + CO_2 + NH_3 + H_2O \rightarrow NaHCO_3 + NH_4Cl \tag{2.8}$$

$NaHCO_3$ is filtered, and the remaining solution of NH_4Cl reacts with the CaO from step 1. The produced $CaCl_2$ is usually used as road salts, and NH_3 is recycled back to the initial reaction of NaCl (reaction step 2).

$$2NH_4Cl + CaO \rightarrow 2NH_3 + CaCl_2 + H_2O \tag{2.9}$$

In a final step, $NaHCO_3$ is converted to Na_2CO_3 (sodium carbonate) by calcination (heating to 160–230 °C) with the loss of water.

$$2NaHCO_3 \rightarrow Na_2CO_3 + H_2O + CO_2 \tag{2.10}$$

Again, the CO_2 can be recycled and reused within the process. This means that the Solvay process consumes only a very small amount of NH_3 and the only ingredients are NaCl and $CaCO_3$ (Figure 2.5).

In terms of pharmaceutical applications, the various salts of sodium, lithium and potassium have the widest use and are discussed in detail in the following sections. These applications range from the use of sodium and potassium salts in dehydration solutions in order to restore replenished mineral balances to the treatment of BD with simple lithium salts.

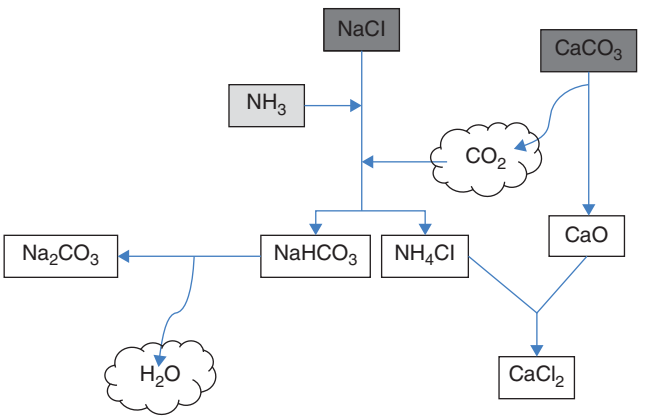

Figure 2.5 *The Solvay process*

2.2 Advantages and disadvantages using lithium-based drugs

The name 'lithium' stems from the Greek word 'lithos' which means stone. Lithium salts are well known for their use in batteries, metal alloys and glass manufacture. Nevertheless, Li also has a clinical application in the treatment of manic depression or BD. BD affects 1–2% of the population and severely reduces the quality of life for the patients and also increases the likelihood of patients committing suicide. Research has shown that lithium salts are very successful in the treatment of BD, and a broad research in this area has been stimulated [3]. The main question addressed within this research is how the lithium ion (Li^+) can be modified in order to improve its activity to patent their findings, which would result in income for the manufacturer. Unfortunately, the simple ion is the active ingredient and this makes it difficult to patent and secure any intellectual property.

Li is a member of group 1 alkali metals and is the lightest and smallest solid element. Li has an atomic number of 3 and contains a single valence electron, which determines its redox chemistry and reactivity. In nature, Li is found as ores, for example, spodumene [$LiAl(SiO_3)_2$], or at low concentrations as salts, for example, in rivers. The metal itself is soft and white in appearance; it has the lowest reactivity within the group of alkali metals. The Li^+ ion has the smallest ionic radius of all known metals.

2.2.1 Isotopes of lithium and their medicinal application

Lithium occurs as mixture of two stable, naturally occurring isotopes (see Section 1.2.1.1), namely ^6Li with an occurrence of 7.59% and the major isotope ^7Li (92.41%). The nucleus of ^6Li contains three protons and three neutrons, whilst ^7Li contains three protons and four neutrons.

^6Li and ^7Li are both NMR (nuclear magnetic resonance) active nuclei, which means their presence can be monitored via NMR technology. Using this analytical tool, it is possible to differentiate between intra- and extracellular Li^+ concentrations and therefore, the uptake of Li^+ into different cells can be monitored. The use of ^6Li results in sharper NMR spectra because of its properties, but it also has a lower intensity. ^6Li salts can also be used to monitor the distribution of lithium in the tissue. A further application of ^6Li is the production of tritium atoms (^3_1H) and their use in atomic reactors. In this process, ^6Li is bombarded with neutrons, which results in the production of tritium atoms and radioactive α-particles (^4_2He):

$$^6_3Li + ^1_0n \rightarrow ^3_1H + ^4_2He \tag{2.11}$$

Equation 2.11 shows the activation of ^6Li.

2.2.2 Historical developments in lithium-based drugs

The first medical use of Li^+ was described in 1859 for the treatment of rheumatic conditions and gout. The theory at that time was based on the ability of lithium to dissolve nitrogen-containing compounds such as uric acid. Their build-up in the body was believed to cause many illnesses such as rheumatic conditions and gout problems. In 1880, Li^+ was first reported as being used in the treatment of BD, and in 1885 lithium carbonate (Li_2CO_3) and lithium citrate [$Li_3C_3H_5O(COO)_3$] were included in the British Pharmacopoeia. It also became clear that there is a direct link between NaCl intake and heart diseases as well as hypertension. Therefore, LiCl was prescribed as replacement for NaCl in the diet of affected patients [3b].

The urea hypothesis and the connection of NaCl to heart diseases stimulated the use of lithium salts in common food. The prime example is the soft drink 7Up©, which has been marketed in 1929 under the label

Bib-Label Lithiated Lemon-Lime Soda. 7Up contained lithium citrate and was also marketed as a hang-over cure. The actual Li^+ was subsequently removed in 1950 [3b].

John Cade's experiments on guinea pigs in 1949 initiated the discovery of Li^+ and its sedative and mood-control properties. Uric acid was known to have mood-controlling properties and Cade used lithium urate as a control solution. To his surprise, he discovered that lithium urate had tranquillising properties, and after further experiments he concluded that this was caused by the lithium ion [4].

Nevertheless, there were drawbacks, especially when the FDA banned Li^+ salts following the death of four US patients. These patients had an average intake of 14 g of lithium chloride (LiCl) per day in order to replace NaCl. Another stumbling stone in the way of success of Li^+ was the discovery of chlorpromazine, the first antipsychotic drug, which is still used for the treatment of BD. In the early 1970s, Li^+ was re-approved by FDA and is now used in 50% of the treatment of BD [5].

2.2.3 The biology of lithium and its medicinal application

Lithium salts are used in the prophylaxis and treatment of mania, and in the prophylaxis of BD and recurrent depression. Lithium therapy is taken orally, usually as lithium carbonate (Li_2CO_3) or lithium citrate [$Li_3C_3H_5O(COO)_3$], with a total dose of up to 30 mmol/day. Li_2CO_3 is the preferred lithium salt used, as it causes the least irritation to the stomach. The treatment has to be closely monitored, and Li^+ blood concentrations are measured 12 h after administration to achieve a serum lithium concentration of 0.4–1 mmol/l. The therapeutic index (concentration window from efficacy to toxicity) for Li^+ is very narrow, and plasma Li^+ concentrations above 2 mM require emergency treatment for poisoning (Figure 2.6) [6].

The administered Li^+ is distributed uniformly in the body tissues and in the blood plasma, with the external cell Li^+ concentration being below 2 mM. Experiments studying the lithium distribution in rats after administration of a high dose of $^6Li^+$ showed that there was no exceptional accumulation of $^6Li^+$ in the brain. $^6Li^+$ distributes fairly uniformly in the body, with bones and endocrine glands showing higher concentrations (Figure 2.7) [7].

Li^+ ions are not soluble in lipids and therefore do not cross plasma membranes. The transport into cells occurs via exchange mechanism by lithium–sodium counter-transport, anion exchange (so-called Li^+/CO_3^{2-} co-transport) and other unrelated transport molecules. The specific mode of action of the simple Li^+ ion is currently unknown, but it is clear that a displacement of Mg^{2+} by Li^+ is involved. Therefore, an alteration of the Mg^{2+} balance in the blood and the urine can be observed in patients treated with Li^+ [3b]. This displacement is actually not surprising because the properties of Li^+ and Mg^{2+} are similar, which can be explained by the concept of *diagonal relationship* (see Section 2.2.4).

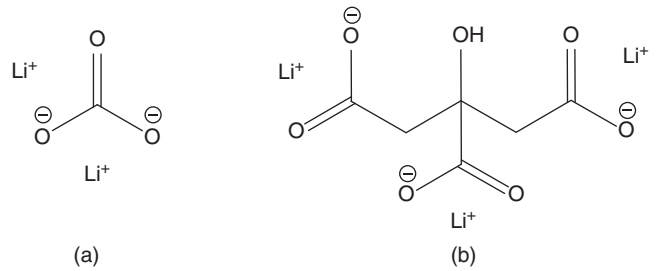

Figure 2.6 *Chemical structures of (a) lithium carbonate and (b) lithium citrate*

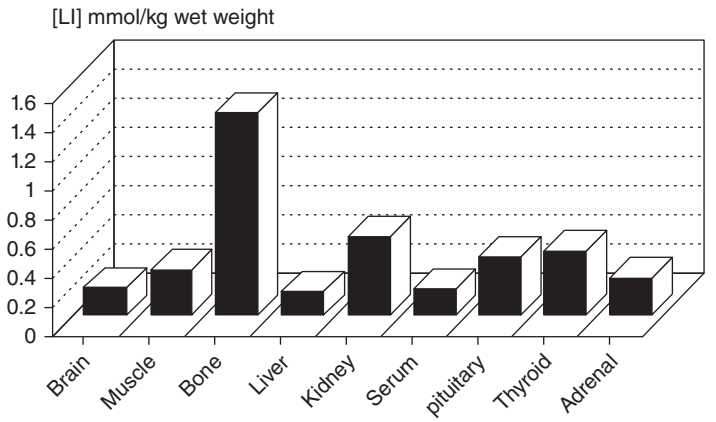

Figure 2.7 *Distribution of $^{6}Li^{+}$ in various tissues of rats after chronic administration [7] (Reproduced with permission from [7]. Copyright © 1999, Royal Society of Chemistry.)*

2.2.4 Excursus: diagonal relationship and periodicity

Within the periodic table, the element pairs Li/Mg, Be/Al, B/Si and others form a so-called *diagonal relationship* to each other. With this concept, similarities in biological activity can be explained as the element pairs have similar properties.

Diagonally adjacent elements of the second and third periods have similar properties – this concept is called ***diagonal relationship****. These pairs (Li/Mg, Be/Al, B/Si, etc.) have similarities in ion size, atomic radius, reactive behaviour and other properties.*

Diagonal relationship is a result of opposite effects, which crossing and descending within the periodic table has. The size of an atom decreases within the same period (from left to right). The reason is that a positive charge is added to the nucleus together with an extra electron orbital. Increasing the nucleus charge means that the electron orbitals are pulled closer to the nucleus. The atomic radius increases when descending within the same group, which is due to the fact that extra orbitals with electrons are added (Figure 2.8) [1].

Trends can be seen for the electronegativity and the ionisation energy; both increase when moving within the same period from left to right and decrease within the same group. Within a small atom, the electrons are located close to the nucleus and held tightly, which leads to a high ionisation energy. Therefore, the ionisation energy decreases within the group and increases within the period (from left to right) – showing the opposite trend compared to the atomic radius. A similar explanation can also be used for summarising the trends seen for the electronegativity: small atoms tend to attract electrons more strongly than larger ones. This means fluorine is the most electronegative element within the Periodic Tables of Elements (Figure 2.9).

This structure of trends is summarised under the term *periodicity of the elements*. This means that within the periodic table, all elements follow the above-mentioned trends in a repetitive way. This allows predicting trends for atomic and ionic radii, electronegativity and ionisation energy (Figure 2.10).

In relation to the diagonal relationship, it becomes clear by studying the described trends that these effects cancel each other when descending within the group and crossing by one element within the PSE. Therefore,

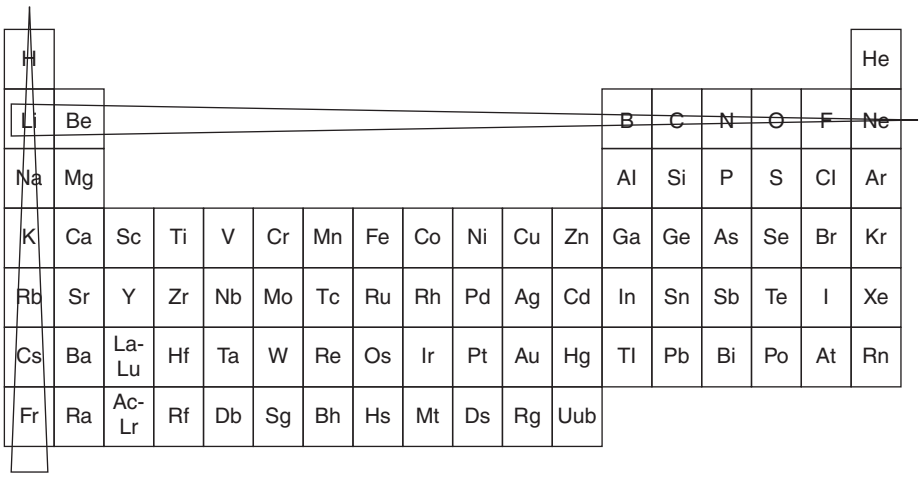

Figure 2.8 *Atomic radii*

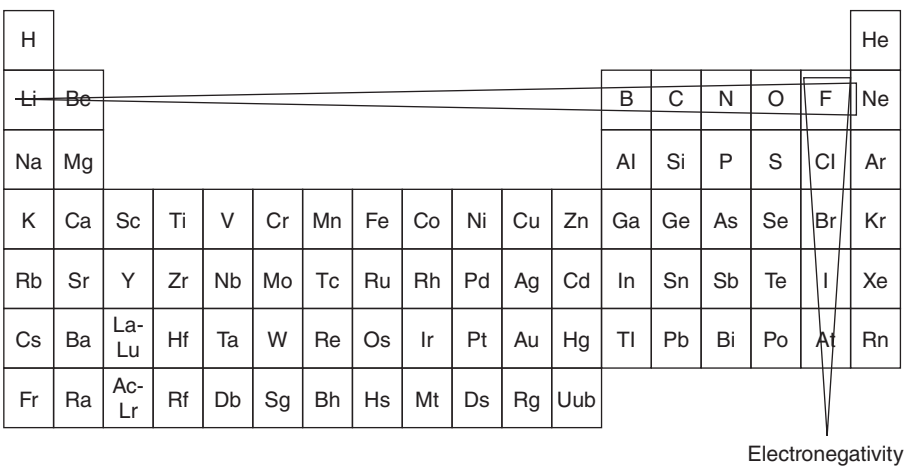

Figure 2.9 *Electronegativity*

elements diagonally positioned within the periodic table have similar properties, such as similar atomic size, electronegativity and ionisation energy (Figure 2.11).

The concept of the diagonal relationship is crucial for the biological activity of lithium drugs, which is mainly due to the properties of the Li^+ ion being similar to the Mg^{2+} ion. In comparison, the size of the Li^+ ion is similar to that of Mg^{2+} and therefore they compete for the same binding sites in proteins. Nevertheless, lithium has relatively specific effects, and so only proteins with a low affinity for Mg^{2+} are targeted. Li^+ and Mg^{2+} salts have similar solubility, for example, CO_3^{2-}, PO_4^{3-}, F^- salts have a low water solubility, and halide and alkyl salts are soluble in organic solvents. Li^+ and Mg^{2+} compounds are generally hydrated, for example, $LiCl{\cdot}3H_2O$ and $MgCl_2{\cdot}6H_2O$. Similarities in ionic size, solubility, electronegativity and solubility result in similar biological activity and therefore pharmaceutical application [3b].

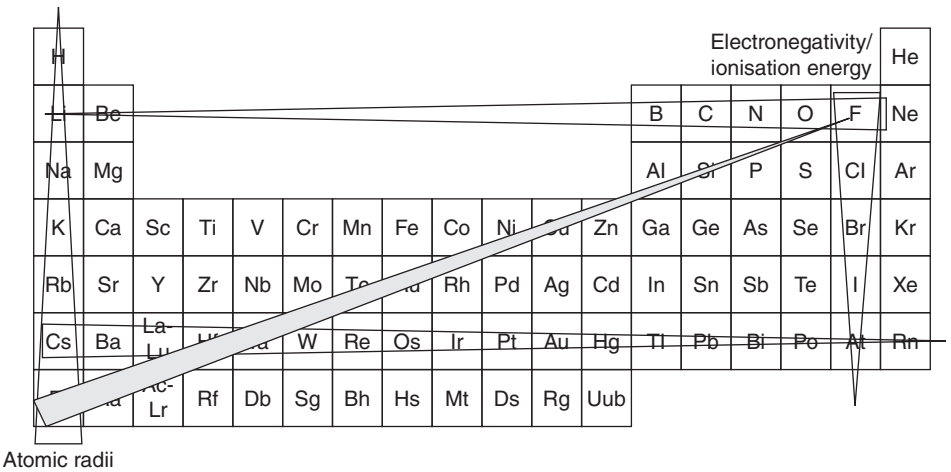

Figure 2.10 *Periodicity showing the 'metallic character' trend (highlighted in grey) within the periodic table*

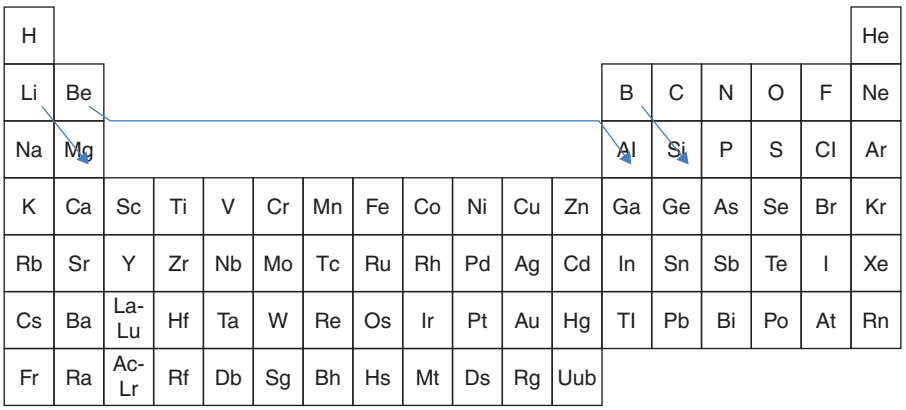

Figure 2.11 *Diagonal relationship*

2.2.5 What are the pharmacological targets of lithium?

The precise mechanism of action of lithium ions as mood stabilisers is unknown. Current research shows that there are two main targets in the cell – the enzymes glycogen synthase kinase-3 (GSK-3) and the phosphomonoesterases family (PMEs) [3b].

GSK-3 is a serine/threonine protein kinase, which is known to play an important role in many biological processes. GSK-3 is an enzyme that mediates the addition of phosphate molecules onto the hydroxyl groups of certain serine and threonine amino acids, in particular cellular substrates. Li^+ inhibits GSK-3 enzymes via competition for Mg^{2+} binding [8].

Phosphoric monoester hydrolases (PMEs) are enzymes that catalyse the hydrolysis of O—P bonds by nucleophilic attack of phosphorous by cysteine residues or coordinated metal ions. Inositol monophosphatase (InsP) is the best known member of this family. Li^+ and Mg^{2+} both have a high affinity to bind to phosphate groups. Li^+ inhibits the enzymatic function of InsP and prevents phosphate release from the active

site. Generally, inositol phosphatases are Mg^{2+}-dependent, but Li^+ binds to one of the catalytic Mg^{2+} sites. Binding Li^+ to phosphate-containing messenger molecules could perturb the transcellular communication and thus be antipsychotic [3b].

Lithium inhibits GSK-3 and InsP, and both pathways have therefore been suggested to be involved in the treatment of BD and schizophrenia. The theory behind this hypothesis is that overactive InsP signalling in the brain of these patients potentially causes BD and this may be reduced by the inhibitory effect of lithium on such signalling [9].

GSK-3 alters structure of cerebella neurons, and lithium is a neuroprotective agent that can reduce the hypersensitivity to toxins as seen in cells that overexpress GSK-3. It is believed that lithium potentially can protect against disease-induced cell death. GSK-3 has been implicated in the origins of schizophrenia, but with the availability of many antipsychotic drugs on the market, lithium ions are not in common use for the treatment of schizophrenia [10].

There are also several direct roles of lithium in the treatment of Alzheimer's disease. Alzheimer's disease is a neurodegenerative brain disorder causing neuronal dysfunction and ultimately cell death. This leads ultimately to dementia, affecting in the United States around 10% of people aged over 65 and 48% aged over 85. Onset occurs with the accumulation of extracellular senile plaques composed of amyloid-β peptides and with the accumulation of intercellular neurofibrillary tangles. GSK-3 is necessary for the accumulation of tangles, and subsequently GSK-3 inhibition reduces the production of peptides – this is where the Li^+ interaction comes into play [3b].

2.2.6 Adverse effects and toxicity

Lithium has a very narrow therapeutic window, which makes the monitoring of blood levels essential during the treatment (see Section 2.2.3). Blood plasma concentrations of more than 1.5 mmol/l Li^+ may cause toxic effects, usually tremors in the fingers, renal impairment and convulsion. Also, memory problems are a very common side effect, and complaints about slowed mental ability and forgetfulness are commonly reported. Extreme doses of lithium can cause nausea and diarrhea, and doses above 2 mmol/l require emergency treatment, as these levels may be fatal. Weight gain and decreased thyroid levels are also commonly reported problems. The blood serum level of Li^+ has to be monitored 12 h after administration, and health care professionals also have to be aware that the mood-stabilising effects of lithium take a couple of days to take effect [6].

Lithium salts have severe adverse effects on the renal system. Lithium therapy can damage the internal structures of the kidneys, which are the tubular structure of the nephrons, and can lead to diabetes insipidus. One out of five patients experience polyuria – excess production of urine, which is the number one symptom of diabetes insipidus. Therefore, the kidney function has to be closely monitored for patients undergoing long-term therapy, with a full test of the kidney function every 6–12 months for stabilised regimes [3a, 6].

Great care has to be taken when lithium is given with nonsteroidal anti-inflammatory drugs (NSAIDs) because up to 60% increase of Li^+ concentration in blood has been observed. NSAIDs reduce the clearance of lithium through kidneys, and as a result lithium poisoning is possible. Furthermore, the concurrent use of diuretics, which can result in sodium depletion, can make lithium toxicity worse and can be hazardous [3a].

2.3 Sodium: an essential ion in the human body

Sodium has atomic number 11 and has the symbol Na, derived from the Latin name 'natrium'. Sodium ions (Na^+) are soluble in water and therefore present in large quantities in the oceans. Na^+ is also part of minerals and an essential element for all animal life.

The main biological roles of sodium ions are the maintenance of body fluids in humans and the functioning of neurons and transmission of nerve impulses. Na^+ is an important electrolyte and a vital component of the extracellular fluid. Therefore, one of its roles is to maintain the fluid in the human body via osmoregulation, a passive transport mechanism (Section 2.3.1). Na^+ ions also play a crucial role in the contraction of muscles and in the mode of action of several enzymes. In the human body, Na^+ is often used to actively build up an electrostatic potential across membranes, with potassium ions (K^+) being the counter-ion (Section 2.3.2). The build-up of an electrostatic potential across cell membranes is important to allow the transmission of nerve impulses.

2.3.1 Osmosis

Osmosis *is defined as the physical process of diffusion of a solvent (water) through a semi-permeable membrane towards an area of high solute (salt) concentration. This means that solvent (water) follows the osmotic gradient by moving across the semi-permeable membrane from one solution where there is a lower salt concentration towards a second solution with a high salt concentration in order to dilute this and to equalise the concentrations.*

Sodium is an essential mineral for the human body and crucial for the regulation of the body fluid via its osmosis activity. Sodium ions account for over 90% of all ions in the plasma and in the interstitial fluid, which are involved in osmosis processes. Furthermore, it is the most abundant cation in the extracellular fluid, and therefore the Na^+ content controls the extracellular volume. In particular, the kidneys play an important role in regulating the fluid level of the body as well as the filtration, secretion and re-absorption of Na^+ in the nephrons, the functional unit of the kidney. Na^+ ions are used in the human body to establish osmotic gradients, which in turn is crucial to control the water balance. Furthermore, decreases in blood pressure and in Na^+ concentrations are sensed by the kidneys, and hormones (e.g. renin, antidiuretic hormones (ADHs), atrial natriuretic peptide) are released that control the blood pressure, osmotic balances and water-retaining mechanisms.

In general, if a medium is

- *hypertonic*, that means the solution has a higher concentration of solutes than the surrounding area. This area will lose water through osmosis;
- *isotonic*, that means the solution has the same concentration of solutes as the surrounding area. No movement of water will occur;
- *hypotonic*, that means the solution has a lower concentration of solutes than the surrounding area. This area will gain water through osmosis (Figure 2.12).

A net movement of the solvent (water) occurs from the hypotonic solution to the solution with the higher concentration in order to reduce the difference in concentrations. The osmotic pressure is defined as the pressure that is required to establish equilibrium with no movement of solvents. It is important to mention that osmotic pressure depends on the number of ions or molecules in the solution, not the identity of those. The unit often being found to describe the osmotic pressure is the osmole (osmol or osm), which is a non-SI unit that defines the numbers of moles of a compound that contributes to the osmotic pressure of a solution.

In general, osmotic processes are important for many biological processes. Plants use osmosis to transport water and solutes through their systems and the osmotic gradient to establish the turgor within cells. The human body uses osmosis for many processes, the excretion of urine being one of the most prominent one.

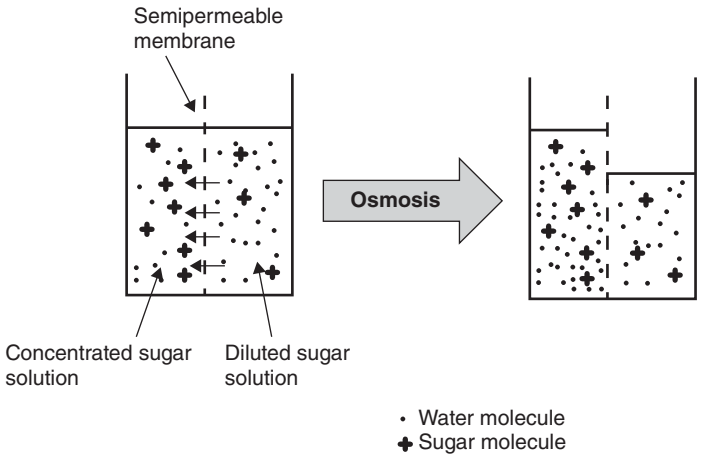

Figure 2.12 *Schematic representation of osmosis*

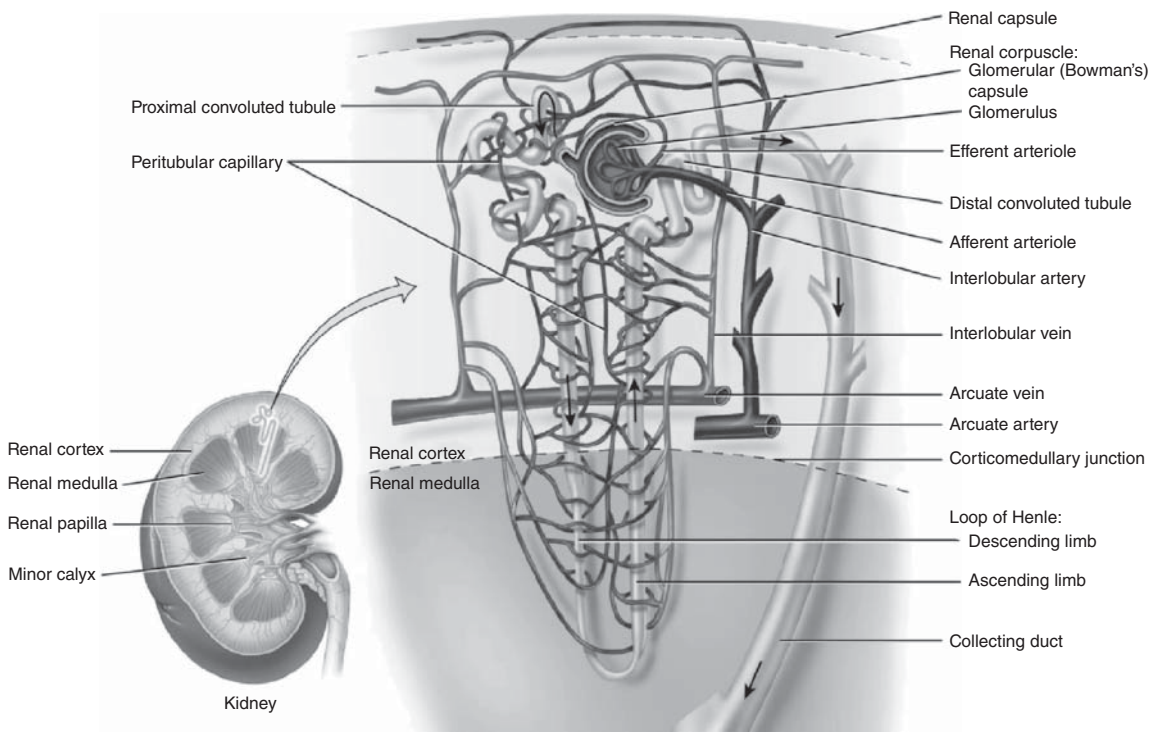

Figure 2.13 *The kidney and its functional unit – the nephron [11] (Reproduced with permission from [11]. Copyright © 2009, John Wiley & Sons, Ltd.)*

Urine production takes place within the kidney, more specifically at the nephrons which are the functional units of the kidneys. Approximately 150–180 of plasma is filtered every day through the glomerulus, which is a part of the nephron, in order to produce the urine. The nephron also consists of the proximal tubule, the Loop of Henle and the distal tubule, which leads to the collecting duct and ultimately to the ureter (Figure 2.13) [11].

Filtration takes places at the glomerulus, whereas the remaining parts of the nephron are responsible for the secretion and re-absorption of ions in order to regulate imbalances and manage the urine volume before the urine is stored in the bladder. This secretion and re-absorption can occur via an active or a passive transport across the nephron membrane. Na^+ is usually actively transported across via Na^+ pumps in order to establish the correct Na^+ concentration in the blood plasma, which is responsible for maintaining the correct osmotic pressure. Via this process, an osmotic gradient is established within the kidney parenchyma, which is used to conserve water. The ascending limb of the Loop of Henle is impermeable to water but permeable to Na^+. As a result, an osmotic gradient is established. The descending limb of the Loop of Henle is permeable to water and, as a result of the osmotic gradient, water moves to the interstitial fluid and urine is concentrated. The collecting ducts can be permeable to water if the body sends out a signal that water has to be conserved. Again, water will passively follow the osmotic gradient and urine will be concentrated even more (Figure 2.14).

2.3.2 Active transport of sodium ions

As previously mentioned, the active transport of sodium ions is crucial for the functioning of, for example, neurons and the subsequent transmission of a nerve impulse. This can be achieved by the active build-up of a concentration gradient along the cell membrane using Na^+/K^+ pumps as the active unit. This active

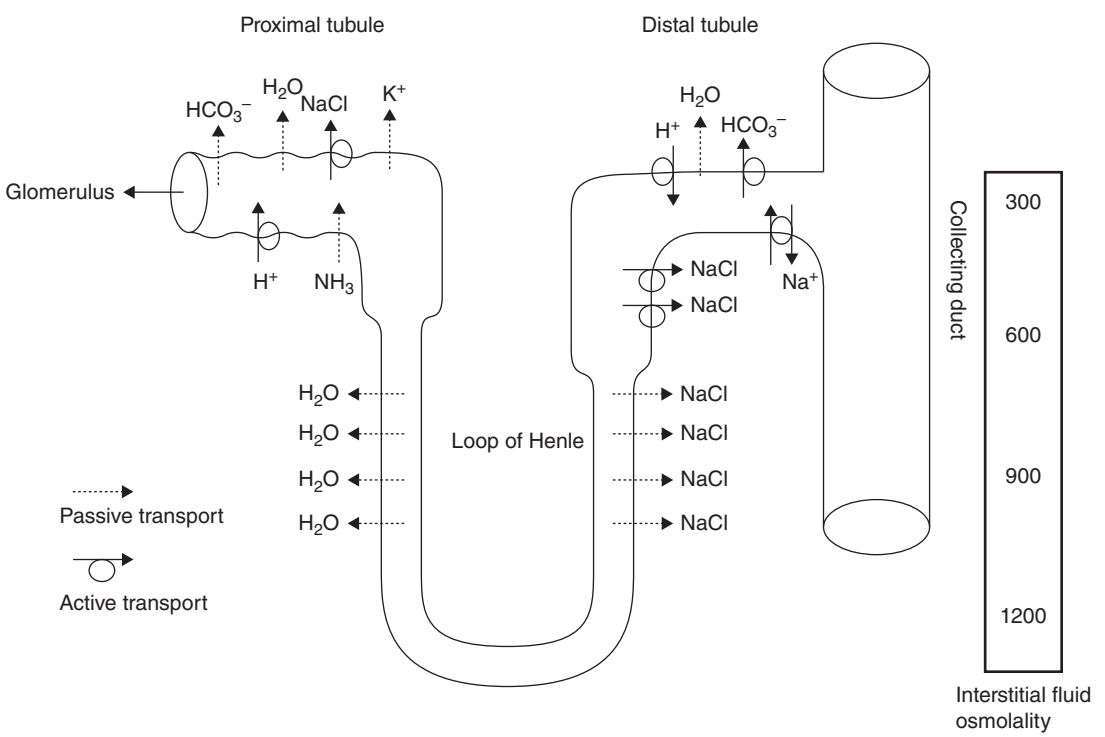

Figure 2.14 *Osmotic gradient in kidney parenchyma*

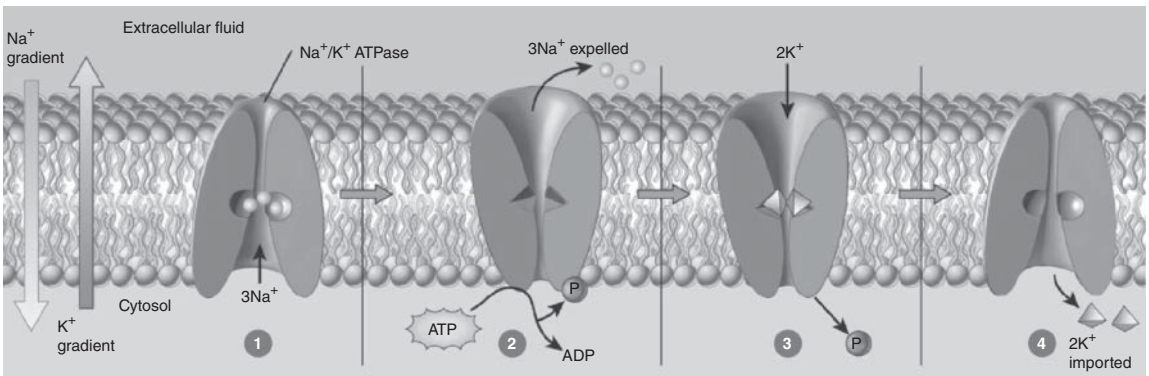

Figure 2.15 *Mode of action of the Na^+/K^+-ATPase [11] (Reproduced with permission from [11]. Copyright © 2009, John Wiley & Sons, Ltd.)*

transport is responsible for the cells containing relatively high concentrations of potassium ions and low concentrations of sodium ions. The resulting electrostatic potential that is built up along the cell membrane is called *action potential* and is subsequently responsible for the transmission of nerve impulses (see Section 2.4.1) (Figure 2.15).

The Na^+/K^+ pumps facilitate an active transport process which is based on the conformational changes of the cross-membrane protein and driven by the breakdown of ATP. In the initial step, three Na^+ ions bind the cross-membrane protein on the cytosolic side. This causes the protein to change its confirmation and makes it accessible to ATP. In its new confirmation, the protein becomes phosphorylated by ATP, which results in a second conformational change. The three Na^+ ions are located across the membrane, and the protein now has a low affinity to the sodium ions. This means that the sodium ions are dissociated from the protein and released into the extracellular fluid. Nevertheless, the protein has now a high affinity to K^+ and binds two potassium ions from the extracellular fluid. The bond phosphate is now dissociated, and the protein reverts back to its original confirmation. This means both K^+ ions are exposed to the cytosol and can be released.

2.3.3 Drugs, diet and toxicity

Sodium chloride solutions are normally used when the patient is diagnosed with sodium depletion and dehydration. Treatment is mostly administered intravenously, but in chronic conditions (mild to moderate sodium loss) sodium chloride or sodium bicarbonate can be given orally. Oral rehydration therapies usually use a mixture of alkali metal-based salts such as NaCl, KCl and their citrates (Figure 2.16) [6].

Sodium bicarbonate is usually administered orally in order to regulate the serum pH. Imbalances of the plasma pH can be due to problems occurring in the kidneys such as renal tubular acidosis. This is a medical condition that occurs where the body accumulates acid as a result of the kidneys failing to regulate the pH of the urine and the blood plasma. Within the kidneys, blood is filtered before it passes through the tubular part of the nephrons where re-absorption or secretion of important salts and others takes place. In renal tubular acidosis, the kidneys either fail to filter or secrete acid ions (H^+) from the plasma (secretion takes place in the distal tubule), or to recover bicarbonate ions (HCO_3^-) from the filtrate (passive re-absorption takes place in the proximal tubule, active re-absorption at the distal tubule), which is necessary to balance the pH. In the view of this mode of action, the pharmaceutically active component of sodium bicarbonate is the bicarbonate anion, but the cation Na^+ is responsible for solubility and compatibility (Figure 2.17) [3a].

The most common dietary source of NaCl is table salt, which is used for seasoning and pickling (the high NaCl content inhibits the bacterial and fungal growth as a result of the osmotic gradient). The daily recommended NaCl intake varies depending on the country and the age group. Within the United Kingdom,

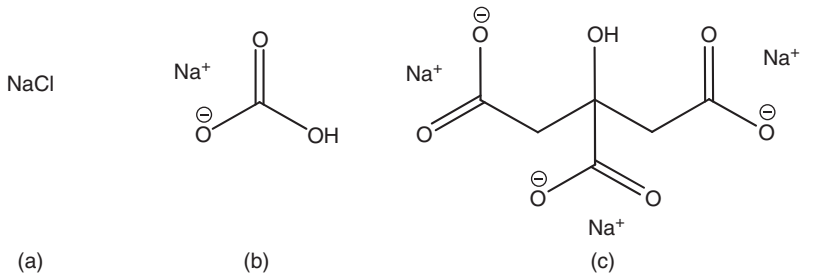

Figure 2.16 *Chemical structures of (a) sodium chloride, (b) sodium bicarbonate and (c) sodium citrate*

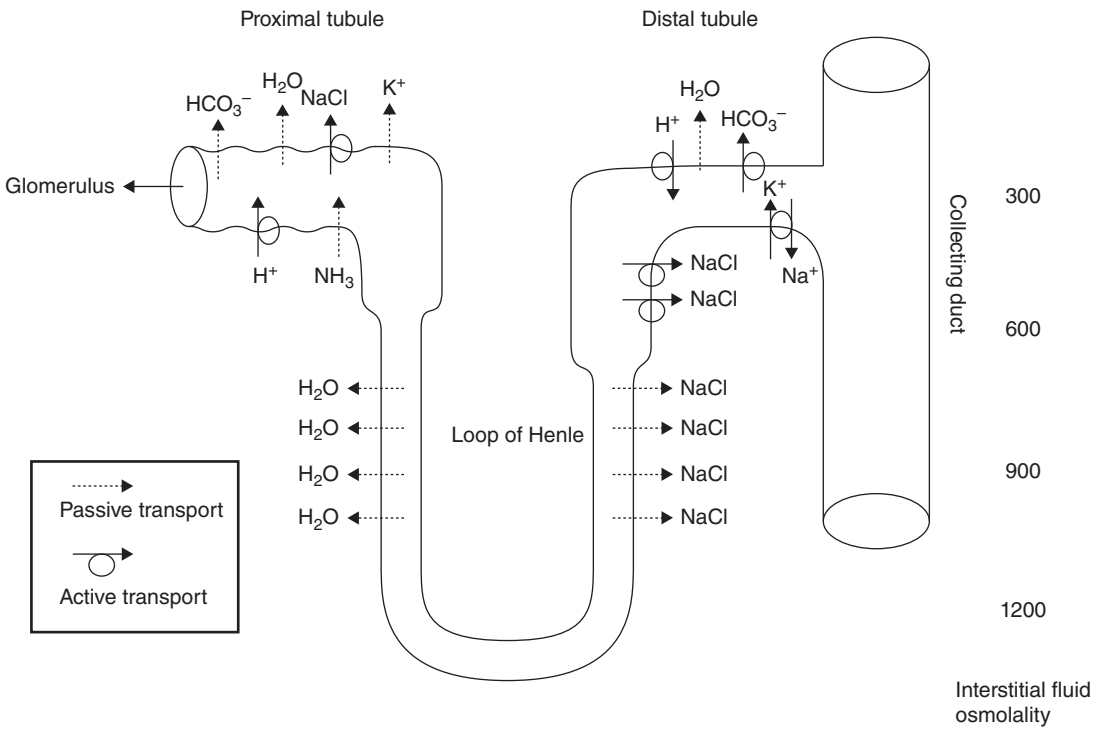

Figure 2.17 *Illustration of a nephron showing areas of active and passive electrolyte transport*

the maximum salt intake is recommended to be limited to 6 g of NaCl for an adult, whereas intake for children should be significantly lower [12]. Most people exceed this amount on a daily basis, and the high salt plasma levels (hypernatraemia) can result in cardiovascular disorders such as hypertension. Low sodium plasma levels (hyponatraemia), which again can be a result of dysfunction kidneys or sodium loss in the bowels, also cause damage to the human body via osmotic imbalances and if necessary have to be treated. Low blood pressure, dehydration and muscle cramps are signs of a sodium deficiency.

Signs of acute toxicity may be seen after ingestion of 500–1000 mg/kg body weight NaCl. These symptoms can be vomiting, ulceration of the gastrointestinal (GI) tract and renal damage. Also, the increased risk for the formation of kidney stones is believed to be a result of high salt intake [13].

2.4 Potassium and its clinical application

Potassium has atomic number 19 and the chemical symbol K, which is derived from its Latin name 'kalium'. Potassium was first isolated from potash, which is potassium carbonate (K_2CO_3). Potassium occurs in nature only in the form of its ion (K^+) either dissolved in the ocean or coordinated in minerals because elemental potassium reacts violently with water (see Section 2.1.3). Potassium ions are essential for the human body and are also present in plants. The major use of K^+ can be found in fertilisers, which contains a variety of potassium salts such as potassium chloride (KCl), potassium sulfate (K_2SO_4) and potassium nitrate (KNO_3). KCl is also found in table salt, whereas potassium bromate ($KBrO_3$) is an oxidising agent and is used as flour improver. Potassium bisulfite ($KHSO_3$) can be used as a food preservative in wine and beer.

2.4.1 Biological importance of potassium ions in the human body – action potential

The so-called action potential occurs in a variety of excitable cells such as neurons, muscle cells and endocrine cells. It is a short-lasting change of the membrane potential and plays a vital role in the cell-to-cell communication. In animal cells, there are two types of action potential. One type is produced by the opening of calcium ion (Ca^{2+}) channels and this is longer lasting than the second type, namely the Na^+-based action potential.

The Na^+/K^+-based action potential is short-lived (only 1 ms) and therefore mostly found in the brain and nerve cells. Potassium ions are crucial for the functioning of neurons, by influencing the osmotic balance between the cells and the interstitial fluid. The concentration of K^+ within and outside the cells is regulated by the so-called Na^+/K^+-ATPase pump. Under the use of ATP, three Na^+ ions are pumped outside the cell and two K^+ ions are actively transported into the cell (see Section 2.3.2). As a result, an electrochemical gradient over the cell membrane is created; the so-called resting potential is established.

In the case of any cell-to-cell communication, changes of the membrane reach a specific part of the neuron first. As a result, sodium channels, which are located in the cell membrane, will open. As a result of the osmotic gradient, which has been established by the Na^+/K^+-pump, Na^+ ions enter the cytosol and the electrochemical gradient becomes less negative. Once a certain level, called the *threshold*, is reached, more sodium channels are opened, and more Na^+ ions flow inside the cell – this creates the so-called action potential. The electrochemical gradient over the cell membrane is thus reversed. Once this happens, the sodium ion channels close and the potassium channels open. The concentration of K^+ in the cytosol is higher than in the extracellular fluid, and therefore potassium ions leave the cell. This allows the cell to shift back to its resting membrane potential. As the membrane potential approaches the resting potential, all voltage-gated K^+ channels open. In actual fact, the membrane repolarises beyond the resting potential; this is known as *hyperpolarisation*. The last step is now to reintroduce the initial balance of sodium and potassium ions. This means that the Na^+/K^+-pump transports Na^+ actively out of the cytosol and K^+ into it. As a result, the initial steady state is reinstated (Figure 2.18).

2.4.2 Excursus: the Nernst equation

As previously outlined, the electric potential across a cell membrane is created by the difference in ion concentration inside and the outside the cell. The *Nernst equation* is an important equation that allows the calculation of the electric potential for *an individual ion.*

$$\Delta E = -\frac{RT}{zF} \ln \frac{[\text{ion}]_{\text{in}}}{[\text{ion}]_{\text{out}}}$$

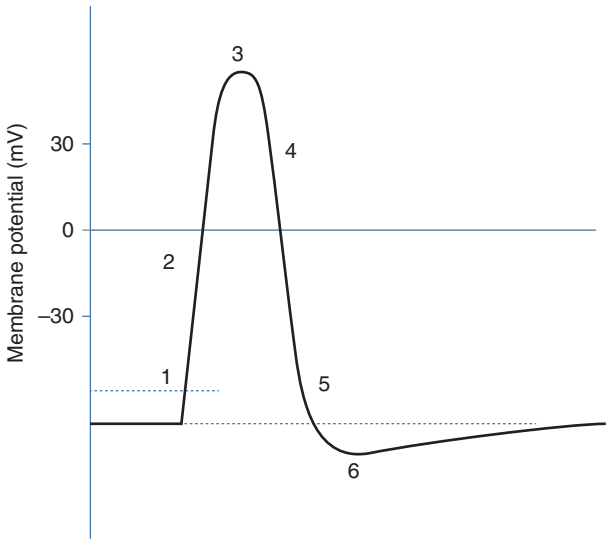

Figure 2.18 *Action potential. (1) Threshold of excitation. Na^+ channels open and allow Na^+ to enter the cell. (2) K^+ channels open and K^+ leaves the cell. (3) No more Na^+ enters cell. (4) K^+ continues to leave the cell. This causes the membrane to return to resting potential. (5) K^+ channels close and Na^+ channels resent. (6) Hyperpolarisation*

Looking at the Nernst equation, R is the gas constant, T is the temperature in kelvin, F is the Faraday constant and z is the net charge of the ion. $[\text{ion}]_{\text{in}}$ and $[\text{ion}]_{\text{out}}$ are the concentration of the particular ion inside and outside the cell. The equation can also be expressed as $\log_{10}$. Furthermore, at room temperature (25 °C), the term $-RT/F$ can be seen as a constant, and the Nernst equation can be simplified:

$$\Delta E = -\frac{0.059}{zV} \log \frac{[\text{ion}]_{\text{in}}}{[\text{ion}]_{\text{out}}}$$

The Nernst equation can also be used to calculate the overall potential in a redox equation by using the ion concentrations of both half-equations. This also allows the calculation of the reduction potential ΔE of *two different ions* of varying concentration. The Nernst equation can be expanded to the following equation, where [Red] and [Ox] represent the concentrations of the reductant and oxidant ($\text{Ox} + \text{e}^- \rightarrow \text{Red}$):

$$\Delta E = E^0 - \frac{0.059}{zV} \log \frac{[\text{Red}]}{[\text{Ox}]}$$

In order to calculate the reduction potential ΔE of *two different ions* of varying concentration, the Nernst equation can be expanded to the following equation:

$$\Delta E = \Delta E^0 - \frac{0.059}{zV} \log \frac{[\text{ion}]_{\text{in}}}{[\text{ion}]_{\text{out}}}$$

It is also possible to calculate the overall electric potential across the cell membrane by taking several different ions into account. The so-called Goldman equation, which will not be further illustrated in this book, can be used to calculate this value.

2.4.3 Potassium salts and their clinical application: hypokalaemia

In the human body, 95% of the K^+ can be found inside the cells, with the remaining 5% mainly circulating in the blood plasma [11]. This balance is carefully maintained by the Na^+/K^+ pump (see Section 2.3.2), and imbalances, such as seen in hypo or hyperkalaemia, can have serious consequences.

Hypokalaemia is a potentially serious condition where the patient has low levels of K^+ in his/her blood plasma. Symptoms can include weakness of the muscles or ECG (electrocardiogram) abnormalities. Mostly, hypokalaemia can be a result of reduced K^+ intake caused by GI disturbance, such as diarrhoea and vomiting, or increased excretion of K^+ caused by diuresis. Hypokalaemia is often found in patients treated with diuretics such as loop diuretics and thiazides. These classes of drugs increase the secretion of Na^+ in the nephrons in order to increase water excretion. Unfortunately, they also increase the excretion of K^+ and lead to hypokalaemia. In contrast, potassium-sparing diuretics actively preserve potassium ions, and patients treated with loop diuretics or thiazides often receive also potassium-sparing diuretics [3a].

Potassium ions are excreted via the kidneys. Within the kidneys, ~150–180 l of plasma is filtered every day through the glomerulus, which is part of the nephron, in order to produce urine. As previously described, the filtration process is followed by a series of processes along the nephron, where a variety of ions are secreted and re-absorbed in order to regulate plasma imbalances and manage the urine volume (Section 2.3.1). K^+ is passively secreted at the proximal tubule and also moves into the interstitial fluid via a counter-flow process to Na^+ mainly at the distal tubule (Figure 2.19).

Oral supplementation in form of potassium salts is especially necessary in patients who take anti-arrhythmic drugs, suffer from renal artery stenosis and/or severe heart failure or show severe K^+ losses due to chronic

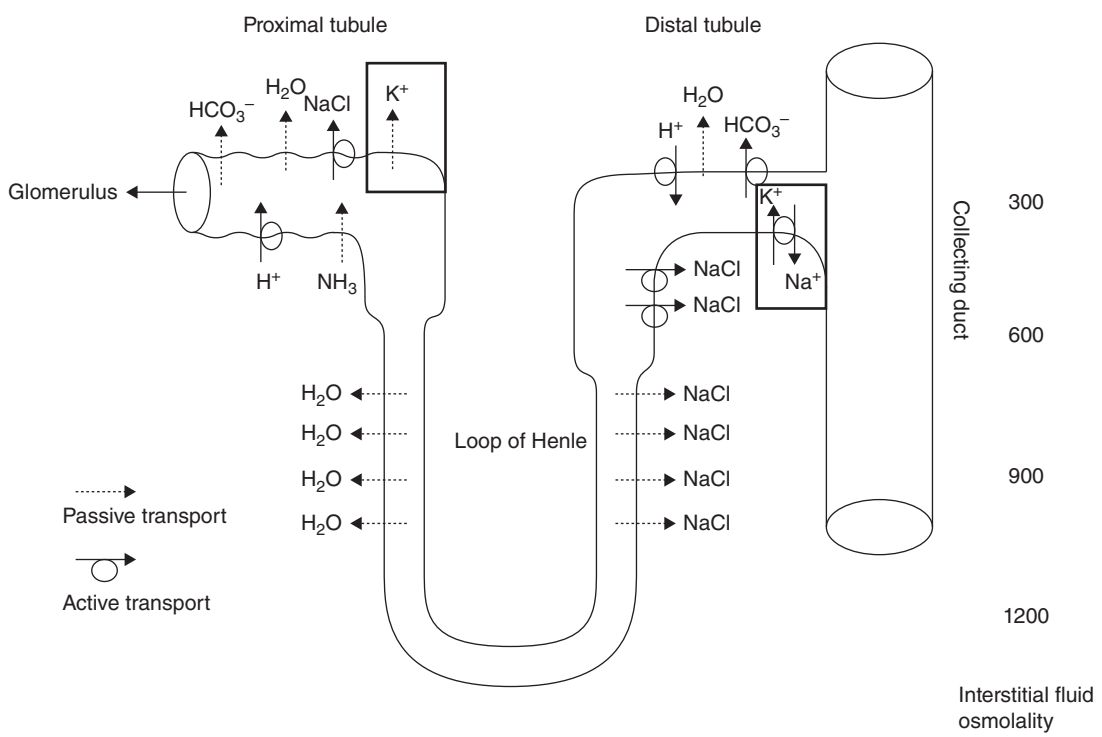

Figure 2.19 *Illustration of a nephron showing areas of potassium transport*

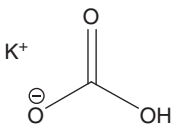

Figure 2.20 *Chemical structure of potassium bicarbonate (KCO_3H)*

diarrhoea or abusive use of laxatives. Regulation of the plasma K^+ level may also be required in the care of elderly patients when the K^+ intake is reduced as a result of changing dietary habits, but special attention has to be given to patients with renal insufficiency because K^+ excretion might be reduced. Potassium salts are preferably given as liquid preparations, and KCl is the preferred salt used. Other potassium-based salts can be used if the patient is at risk of developing hyperchloraemia – increased chloride plasma levels. Typically potassium salts are dissolved in water, but the salty and bitter taste makes them difficult to formulate. Oral bicarbonate solutions such as potassium bicarbonate are typically given orally for chronic acidosis states – low pH of the blood plasma. This can be again due to impaired kidney function. The use of potassium bicarbonate for the treatment of acidosis has to be carefully evaluated, as even small changes of the potassium plasma levels can have severe consequences (Figure 2.20) [3a].

Potassium citrate is used in the United Kingdom as an over-the-counter drug for the relief from discomfort experienced in mild urinary-tract infections by increasing the urinary pH. It should be not given to men if they experience pain in the kidney area (risk of kidney stones) or if blood or pus is present in the urine. Also, patients with raised blood pressure or diabetes should avoid taking potassium citrate without consultation with their general practitioner (GP). Caution is generally advised to patients with renal impairment, cardiac problems and the elderly [3a].

2.4.4 Adverse effects and toxicity: hyperkalaemia

The therapeutic window for K^+ in the blood plasma is very small (3.5–5.0 mmol), and especially hyperkalaemia, an increased level of K^+ in the plasma, can lead to severe health problems [11]. Potassium salts can cause nausea and vomiting and in extreme cases can lead to small bowel ulcerations. Acute severe hyperkalaemia is defined when the plasma potassium concentration exceeds 6.5 mmol/l or if ECG changes are seen. This can lead to cardiac arrest, which needs immediate treatment. Treatment options include the use of calcium gluconate intravenous injections, which minimises the effects of hyperkalaemia on the heart. The intravenous injection of soluble insulin promotes the shift of potassium ions into the cells. Diuretics can also be used to increase the secretion of K^+ in the kidneys, and dialysis can be a good option if urgent treatment is required. Ion-exchange resins, such as polystyrene sulfonate resins, may be used in mild to moderate hyperkalaemia to remove excess potassium if there are no ECG changes present. As previously mentioned, especially in patients suffering from kidney diseases or end-stage renal failure, the potassium levels have to be monitored very carefully and corrected if necessary. Potassium excretion is likely to be disturbed, and a build-up of potassium in the blood plasma may trigger a cardiac arrest [3a].

Potassium salts are also available in the form of tablets or capsules for oral application especially as nonprescription medicine. Usually, their formulation is designed to allow the potassium ions to be slowly secreted, because very high concentrations of K^+ are known to be toxic to tissue cells and can cause injury to the gastric mucosa. Therefore, nonprescription potassium supplement pills are usually restricted to <100 mg of K^+ [6].

2.5 Exercises

2.5.1 Determine the oxidation state for all elements in the following molecules:

(a) H_2O
(b) NaCl
(c) H_2O_2
(d) Fe_2O_3
(e) MnO_4^-
(f) $Cr_2O_7^{2-}$
(g) SiH_4

2.5.2 Complete the reduction and oxidation equation and write the redox equation in the following examples:

(a) $MnO_4^- + Fe^{2+} + ???? \rightarrow Mn^{2+} + Fe^{3+} + ??????$ under acidic conditions

(b) $MnO_4^- + Br^- + OH^- \rightarrow ??? + BrO_3^-$ under basic conditions

(c) $Cr_2O_7^{2-} + Cu^+ \rightarrow Cu^{2+} + ???$ under acidic conditions

(d) $IO_3^- + I^- \rightarrow I_2$ under acidic conditions

2.5.3 Complete the equation and indicate the standard reduction potential E^0_{red} assuming both reactions partners are used in the same concentration.

(a) $Br_2 + 2I^- \rightarrow ????$ $E_0(Br_2/Br^-) = 1.07\,V$
$E_0(I_2/I^-) = 0.54\,V$

(b) $Fe^{2+} + Ce^{4+} \rightarrow ????$ $E_0(Ce^{4+}/Ce^{3+}) = 1.61\,V$
$E_0(Fe^{3+}/Fe^{2+}) = 0.77\,V$

(c) $Br_2 + Fe \rightarrow ????$ $E_0(Br_2/Br^-) = 1.07\,V$
$E_0(Fe^{2+}/Fe) = -0.44\,V$

2.5.4 Calculate *E* for the following redox pair when $Mn^{3+} = 0.5$ M and $Mn^{2+} = 0.01$ M [$E_0(Mn^{3+}/Mn^{2+}) = 1.51$ V] using the Nernst equation.

2.6 Case studies

2.6.1 Lithium carbonate (Li_2CO_3) tablets

Your pharmaceutical analysis company has been contacted by an important client and asked to analyse a batch of formulated Li_2CO_3 tablets. The description of your brief states that you are supposed to analyse the API in these tablets following standard quality assurance guidelines.

Typical analysis methods used for quality purposes are based on titration reactions. A certain amount of powdered Li_2CO_3 tablets is dissolved in water, and a known amount of HCl is added. The solution is boiled to remove any CO_2. The excess acid is then titrated with NaOH using methyl orange as an indicator [14].

(a) Research the type of titration described. Describe the chemical structure and mode of action of the indicator.
(b) Formulate the relevant chemical equations.
(c) The package states that each tablet contains 250 mg Li_2CO_3. For the experiment, 20 tablets are weighed and powdered (total weight 9.7 g). Powder containing 1 g of Li_2CO_3 is dissolved in 100 ml water, and 50 ml of 1 M HCl is added. After boiling, the solution is titrated against 1 M NaOH using methyl orange as the indicator. For each titration, the following volume of NaOH was used:

35.0 ml	35.5 ml	34.5 ml

Calculate the amount of Li_2CO_3 present in your sample. Express your answer in grams and moles.
(d) Critically discuss your result in context with the stated value for the API.
(e) Research and critically discuss the typically accepted error margins.

2.6.2 Sodium chloride eye drops

Your pharmaceutical analysis company has been contacted by an important client and asked to analyse a batch of eye drops containing a NaCl solution. The description of your brief states that you are supposed to analyse the API in these tablets following standard quality assurance guidelines.

Typical analysis methods used for quality purposes are based on titration reactions. A certain volume of NaCl solution is titrated with silver nitrate ($AgNO_3$). Potassium chromate is used as the appropriate indicator [14].

(a) Research the type of titration described. Describe the chemical structure and mode of action of the indicator.
(b) Formulate the relevant chemical equations.
(c) The package states that the eye drops are a 0.9% w/v aqueous solution of NaCl. For the experiment, a volume containing 0.1 g of NaCl is titrated with a 0.1 M $AgNO_3$ solution. For each titration, the following volume of $AgNO_3$ is used:

16.9 ml	17.0 ml	17.4 ml

Calculate the amount of NaCl present in your sample. Express your answer in grams and moles.
(d) Critically discuss your result in context with the stated value for the API.
(e) Research the typically accepted error margins.

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