6

Group 15 Elements

Members of group 15 of the periodic table (15th vertical column) are summarised as group 15 elements (or the nitrogen group) consisting of nitrogen (N), phosphorus (P), arsenic (As), antimony (Sb) and bismuth (Bi) (Figure 6.1).

The appearance of group 15 elements varies widely, reflecting the changing nature of the elements when descending within the group from nonmetal to metal. This trend can be seen both in their structures as well as in their chemical and physical properties. Nitrogen is a colourless and odourless gas. Phosphorous exists as white, red and black solids, whereas arsenic is found as yellow and grey solids. Antimony presents itself in a metallic grey form, and bismuth is a white crystalline metal.

Nitrogen atoms are included in a variety of organic drugs, and their application will not further be discussed in this book. Phosphorus is also an essential element for human life, and some of its biochemical uses as well as clinical applications will be discussed in Section 6.2. The clinical use of arsenic is known as the *start of chemotherapy*. Arsenic, despite its known toxicity, is still clinically used to combat a variety of diseases including cancer (see Section 6.3).

6.1 Chemistry of group 15 elements

6.1.1 Occurrence and extraction

Nitrogen makes up 78% (by volume) of air, whereas phosphorus can be found in several minerals and ores. Phosphorus is an essential constituent of plants and animals, being present in deoxyribonucleic acid (DNA), bones, teeth and other components of high biological importance. Phosphorus does not occur in its elemental state in nature, as it readily oxidises and therefore is deposited as phosphate rock. The remaining elements of group 15 are mostly obtained from minerals, but can also be found in their elemental form in the earth's crust. Arsenic is mostly presented in nature as mispickel (FeAsS), realgar (As_4S_4) and orpiment (As_2S_3). Bismuth occurs as bismuthinite (Bi_2S_3) as well as in its elemental form.

Dinitrogen (N_2) is extracted by fractional distillation of liquid air. By-products such as dioxygen (O_2) are removed by addition of H_2 and the use of a Pt catalyst. Elemental phosphorus is extracted from phosphate

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H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La-Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac-Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub						

Figure 6.1 *Periodic table of elements. Group 15 elements are highlighted*

rock by reacting with sand and coke in an electrically heated industrial oven. Phosphorus vapour is isolated and condensed under water – white phosphorus is extracted.

$$2Ca_3(PO_4)_2 + 6SiO_2 + 10C \rightarrow P_4 + 6CaSiO_3 + 10CO$$

Elemental arsenic is extracted mainly from FeAsS by heating and subsequent condensation of arsenic in the absence of air.

$$FeAsS \rightarrow FeS + As \quad \text{(in absence of air)}$$

Antimony is obtained from stibnite (Sb_2S_3) after reduction with iron. Bismuth is extracted from its sulfide or oxide ores via a reduction with carbon.

$$Sb_2S_3 + 3Fe \rightarrow 2Sb + 3FeS$$

6.1.2 Physical properties

The physical properties of group 15 elements vary widely, from nitrogen being a gas to the remaining elements being solids with increasing metallic character. Nitrogen exists as a diatomic molecule N_2 and is a colourless and odourless gas (condensation at 77 K). Nitrogen forms relatively strong and short bonds, resulting in the formation of a triple bond in the N_2 molecule. Furthermore, nitrogen has an anomalously small covalent radius and therefore can form multiple bonds with N, C and O atoms. Group 15 elements follow the general trend showing an increasing covalent radius when descending within the group.

Phosphorus has several allotropes, with white, red and black phosphorus being the main ones.

> ***Allotropes*** *are defined as the two or more physical forms of one element. Allotropes of carbon are graphite, carbon and diamond. These allotropes are all based on carbon atoms but exhibit different physical properties, especially with regard to hardness.*

White phosphorus is a solid consisting of tetrahedral P_4 molecules with single bonds. White phosphorus is the standard state of the element, but it is metastable, potentially due to the strained 60° bond angles (Figure 6.2).

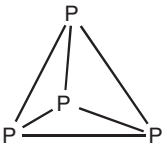

Figure 6.2 *Structure of white phosphorus*

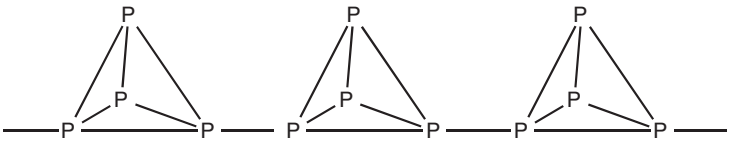

Figure 6.3 *Structure of red phosphorus*

Heating of white phosphorus in an inert gas atmosphere results in red phosphorus, which is an amorphous solid (several crystalline forms are known) with an extended covalent structure (Figure 6.3).

Black phosphorus is the most stable allotrope of phosphorus and can be obtained by heating white phosphorus under high pressure. In contrast to white phosphorus, black phosphorus does not ignite spontaneously in air. The reactivity of red phosphorus lies between those of the white and black allotropes. White phosphorus is insoluble in water and is therefore stored under water to prevent oxidation.

Arsenic and antimony vapour consists of As_4 or Sb_4 molecules, respectively. In the solid state, arsenic, antimony and bismuth are grey solids with a lattice structure similar to that of black phosphorus.

6.1.3 Oxidation states and ionisation energy

The general electron configuration for group 15 elements is ns^2np^3 and all elements form the oxidation states of +3 and +5. Nitrogen is more versatile and shows a range of oxidation states ranging from −3 to +5.

The ionisation energies relating to the removal of the first five electrons (two s and three p electrons) are relatively low. There is a significant increase in the ionisation energy necessary for the removal of a sixth electron, as this will be removed from an inner complete quantum shell (Table 6.1).

Table 6.1 *Ionisation energies (kJ/mol) for group 14 elements [1]*

	First	Second	Third
N	1 403	2857	4578
P	1 012	1897	2910
As	947	1950	2732
Sb	834	1596	2440
Bi	703	1610	2467

Source: Reproduced with permission from [1]. Copyright © 1996, John Wiley & Sons, Ltd.

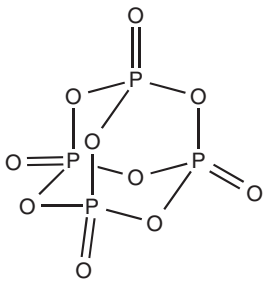

Figure 6.4 *Chemical structure of phosphorus(V) oxide*

6.1.4 Chemical properties

Nitrogen is relatively unreactive because the bond enthalpy of the nitrogen–nitrogen triple bond is very high (944 kJ/mol). $N_2(g)$ is usually used as an inert atmosphere for reactions that cannot be carried out in oxygen. Only lithium reacts directly with nitrogen with the formation of Li_3N. *Nitrogen fixation* is an important mechanism developed by some microorganism in order to directly incorporate nitrogen gas into proteins. This process is an important step in the early food chain.

There are five *oxides* of nitrogen known – N_2O, NO, N_2O_3, NO_2 and N_2O_5 (oxidation numbers ranging from +1 to +5, respectively). Nitric(III) acid (nitrous acid) HONO and nitric(V) acid (nitric acid) HNO_3 are the most important oxoacids of nitrogen. HNO_3 is a highly reactive oxidising and nitrating agent.

In general, phosphorus is more reactive than nitrogen. White phosphorus ignites spontaneously in air and forms phosphorus(V) oxide. Phosphoric acid (H_3PO_4) is the most important oxoacid of phosphorus and its main use is in the manufacture of fertilisers (Figure 6.4).

Hydrogen-containing compounds of nitrogen and phosphorus, namely NH_3 and PH_3, both act as a Lewis base because of their lone pair. Phosphine (PH_3) is less water soluble than NH_3 as it does not form hydrogen bonds. NH_3 (ammonia) is produced in the so-called Haber Bosch process. This industrial process uses finely divided iron as catalyst and a reaction temperature of around 450 °C at a pressure of 50 atm. Ammonia is used to produce fertilisers, nitric acid, nylon and many more products important to our modern life style.

$$N_2(g) + 3H_2(g) \rightarrow 2NH_3(g)$$

For clinical applications, nitrogen and phosphorus compounds are mostly used as heteroatoms in organic compounds or counter-ions in inorganic salts with no specific therapeutic effect. Arsenic differs because it exhibits its own typical therapeutic and toxic properties, which has resulted in its long-standing use in clinical applications and in the invention of chemotherapy. Therefore, the following clinical discussion will concentrate on arsenic-based drugs.

6.2 Phosphorus

Phosphorus (P) is a nonmetal of the nitrogen group. As previously outlined, +3 and +5 are the preferred oxidation states, forming a variety of allotropes, with black phosphorus being the most stable one. Phosphorus is one of the most abundant elements in the human body and is often found in conjunction with calcium, because together they are the building materials for bones and teeth. Phosphorus is also involved in the building of our genetic material as well as in the energy supply of cells and many biochemical processes.

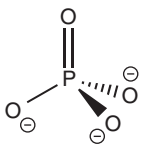

Figure 6.5 *Chemical structure of phosphate*

Within the human body, phosphate is the main phosphorus-containing compound. Phosphate is an inorganic compound and is the salt of phosphoric acid. It can form organic esters with a variety of compounds and these are important in many biochemical processes. Phosphate has the empirical formula PO_4^{3-}. It is a tetrahedral molecule, where the central phosphorus atom is surrounded by four oxygen atoms (Figure 6.5).

The phosphate ion PO_4^{3-} is the conjugated base of the hydrogen phosphate ion (HPO_4^{2-}). HPO_4^{2-} is the conjugated base of the dihydrogen phosphate ion ($H_2PO_4^-$). The latter is the conjugated base of phosphoric acid (H_3PO_4).

*A **conjugated base** is formed from an acid by the removal of a proton. This means that the conjugate base of an acid is this acid without a proton. An analogous definition applies to a conjugate acid.*

$$\text{A conjugate base (of the acid)} + H^+ \rightarrow \text{Acid}$$

$$\text{A conjugate acid (of the base)} \rightarrow \text{Base} + H^+$$

In biological systems, phosphate is often found either as the free ion (inorganic phosphate) or as an ester after reaction with organic compounds (often referred to as *organic phosphates*). Inorganic phosphate (mostly denoted as P_i) is a mixture of HPO_4^{2-} and $H_2PO_4^-$ at physiological pH.

6.2.1 Adenosine phosphates: ATP, ADP and AMP

Adenosine phosphates are organic-phosphate-containing compounds that are responsible for the energy flow in many biochemical processes in living cells. Adenosine phosphates consist of three parts: a sugar molecule (ribose) as the backbone, to which a nucleobase adenine and a varying number of phosphate groups are connected. Adenine is bonded to C-1 of the sugar, whilst the phosphate groups are connected to each other and then are attached to the C-5 atom of the ribose backbone. There is a series of adenosine phosphates depending on the number of phosphate groups present. Adenosine triphosphate (ATP) contains three phosphate groups, whilst adenosine diphosphate (ADP) contains two and adenosine monophosphate (AMP) contains one phosphate group (Figure 6.6) [2].

Within living cells, energy is transferred by dephosphorylation of ATP, which results in a transfer of energy to biochemical processes and the production of ADP. The enzyme ATPase is used to cleave off the phosphate group.

6.2.2 Phosphate in DNA

DNA is a major macromolecule in all living organism responsible for the encoding of genetic material. Mostly, DNA consists of a double-stranded helix. Each strand has a backbone of alternating sugar moieties (deoxyribose) and phosphate groups. The phosphate group is attached to 5′ position of the deoxyribose (Figure 6.7).

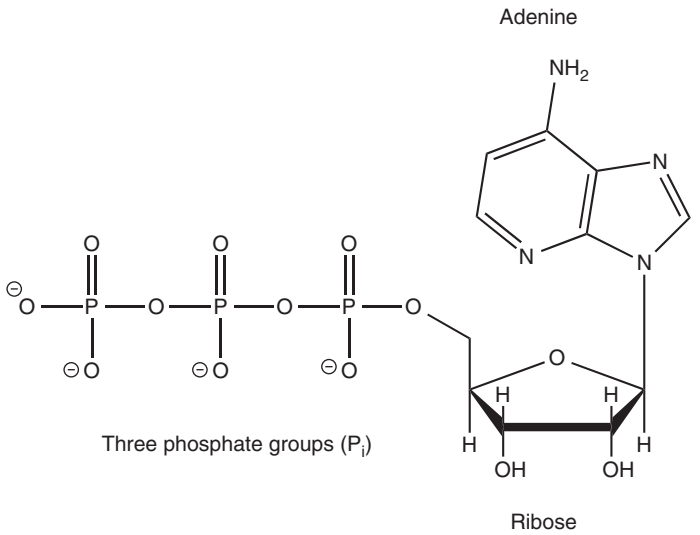

Figure 6.6 *Chemical structures of ATP*

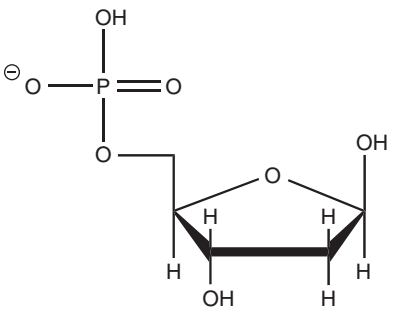

Figure 6.7 *DNA backbone*

There is also an organic base attached to the sugar moiety in the 1′ position. In DNA, these organic bases are thymine (T), cytosine (C), adenine (A) or guanine (G) (Figure 6.8). This unit, the deoxyribose with the phosphate group and a base, is called a *nucleotide* (Figure 6.9).

These nucleotides are then joined together by a condensation reaction of the phosphate and the hydroxyl group in 3′ position (Figure 6.10).

As previously mentioned, DNA mostly exists as a double-stranded helix. The double strand is formed by the interaction between the base pairs. Adenine and thymine form two hydrogen bonds, whereas guanine and cytosine are held together by three hydrogen interactions (Figure 6.11).

It is important to note that the two strands run in opposite directions. Whilst one strand runs in the 5′–3′ direction, the other one runs in the 3′–5′ direction.

6.2.3 Clinical use of phosphate

Phosphorus-containing compounds, mainly phosphates, are usually present in abundance in the human diet. They are mostly found in milk, meat (protein-rich food), grains, dried fruits and carbonated soft drinks.

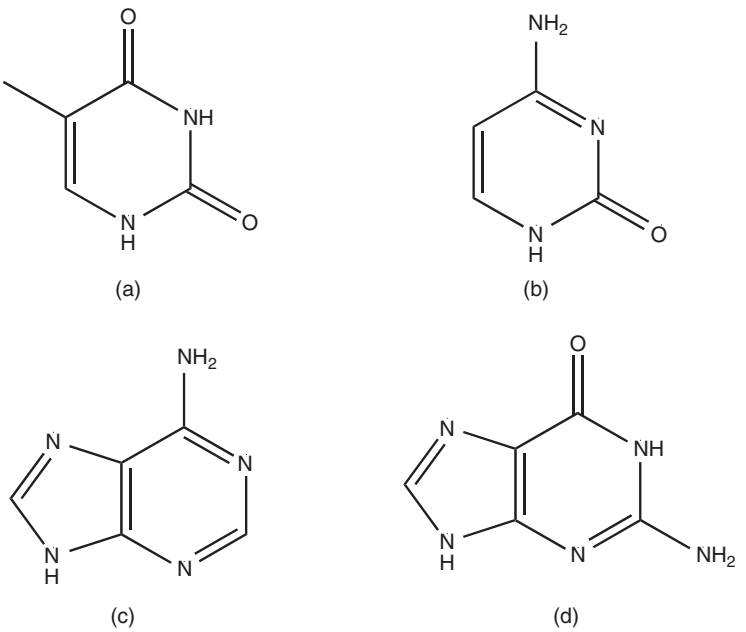

Figure 6.8 *Chemical structures of bases: (a) thymine, (b) cytosine, (c) adenine and (d) guanine*

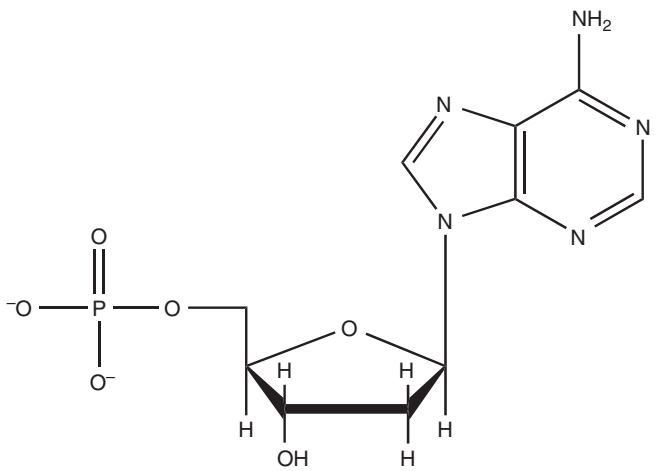

Figure 6.9 *Chemical structure of the nucleotide adenine*

Hypophosphataemia (low levels of phosphate in the serum) is rare and is often caused by some underlying illness, extreme lifestyle situations such as starvation or alcoholism or drug interactions; for example, some diuretics may cause low phosphate levels. Hyperphosphataemia, in contrast, is more common and often caused by kidney problems (reduced clearance) or dietary behaviour (increased intake). Phosphate and calcium ions work closely together and therefore an imbalance of either ion can have serious consequences for bone health or can even lead to cardiovascular problems due to hardening of the soft tissue [2, 3].

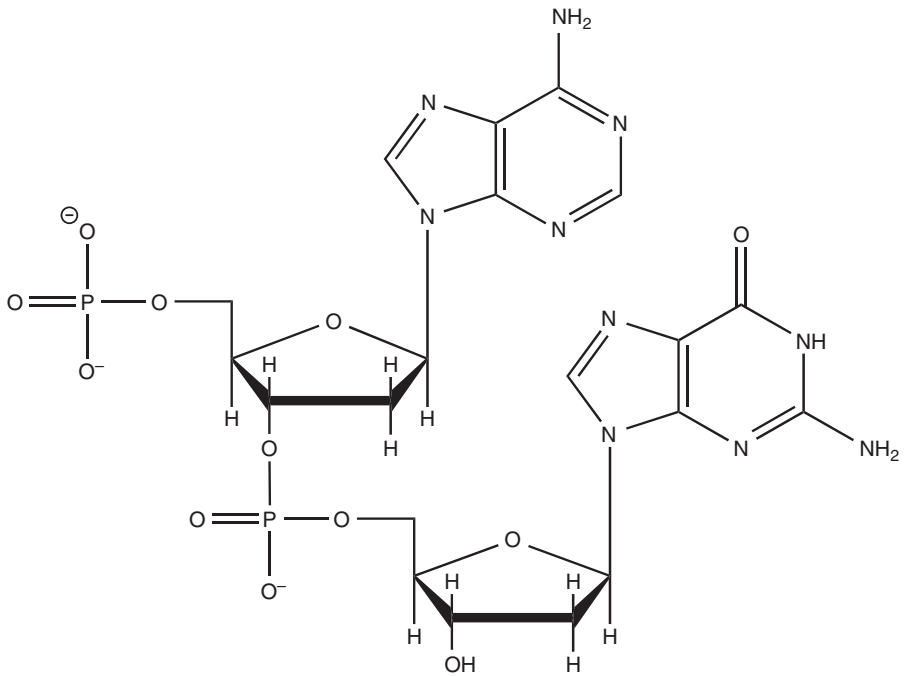

Figure 6.10 *Result of the condensation reaction of the phosphate and the hydroxyl group in 3′ position*

The recommended daily allowance for dietary phosphate ranges between 700 and 1250 mg depending the circumstances, and typically no supplementation in healthy humans is necessary [4]. Phosphate supplementation should be taken only under medical supervision and is usually indicated in the following cases: Hypophosphataemia, hypercalcaemia (high levels of blood Ca^{2+} levels) and sometimes for calcium-based kidney stones. Oral phosphate supplementation will be needed only in a minority of patients, often in patients dependent on alcohol or with severe underlying medical conditions. Oral phosphate tablets and solutions typically contain a mixture of monobasic sodium phosphate, sodium dihydrogen phosphate and/or disodium phosphate. Intravenous (IV) preparations containing phosphate together with potassium and sodium ions can be used in extreme cases of hypophosphataemia [5].

Phosphate solutions can also be used in enemas, where they display their laxative properties. Phosphate enemas are used for the clearance of the bowel before any surgery or endoscopy. A typical phosphate enema solution contains a mixture of sodium dihydrogen phosphate and hydrated disodium phosphate (Figure 6.12) [5].

Hyperphosphataemia is a more common problem seen in patients either because of excessive intake of phosphate or owing to reduced renal clearance such as in patients with renal failure. In this case, phosphate binding agents are used to treat the patients to manage high blood phosphate levels. Mostly, calcium preparations (e.g. calcium citrate tablets or capsules) are used as phosphate binding agents. The aim is to bind any excess phosphate in the gut before absorption. In patients on dialysis, Sevelamer or lanthanum salts (see Chapter 11) can be used to maintain normal phosphate blood levels. Sevelamer is a polymer containing amine groups. These protonated amine groups can react with the negatively charged phosphate groups via ionic binding and prevent absorption of phosphate from the gut. In the past, aluminium preparations were used, but they are not recommended anymore because of potential aluminium accumulation (see Chapter 4) [5].

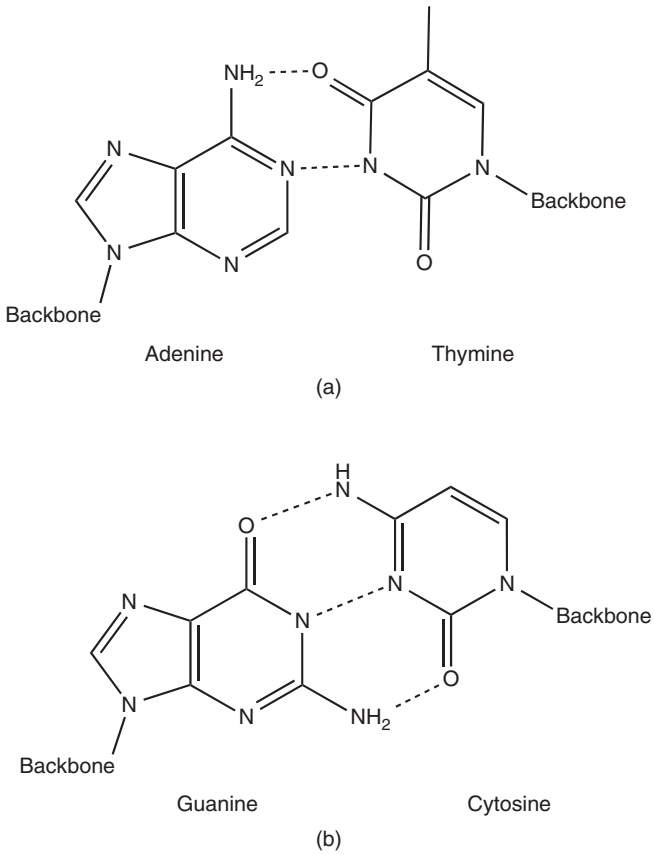

Figure 6.11 *Illustration of base pairing. (a) A–T base pair and (b) G–C base pair*

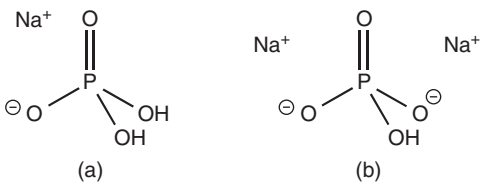

Figure 6.12 *Chemical structures of sodium dihydrogen phosphate (a) and disodium phosphate (b)*

Bisphosphonates are structural analogues to pyrophosphate and contain two phosphate groups linked together by a central carbon centre containing an organic side chain. The phosphonate is absorbed onto the hydroxyapatite crystals in the bone, thereby slowing down any metabolic processes in the bone. The side chain influences the skeletal binding and prevents the enzymatic breakdown in the gastrointestinal tract by phosphatases.

Bisphosphonates are mainly licensed for the treatment of osteoporosis, and alendronic acid is mostly the drug of choice. Administration typically is by mouth as tablets once a day or once a week for post-menopausal

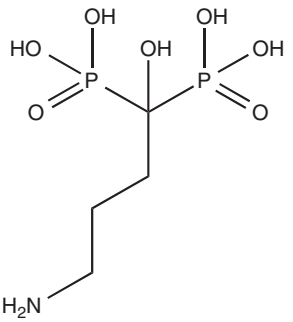

Figure 6.13 *Chemical structure of alendronic acid as an example of a bisphosphonate*

women [5]. It is interesting to note that the oral bioavailability of bisphosphonates, which are typically large hydrophilic molecules, is very low with only up to 1.5% of the administered dose [6]. Bisphosphonates are large hydrophilic molecules, which prevents their diffusion through the transcellular route [7]. Additionally, the negative charges hinder other absorption mechanisms and encourage reaction with positively charged ions and molecules (Figure 6.13).

Bisphosphonates can also be used for the treatment of hypercalcaemia and pain from metastatic bone cancer in patients with breast cancer. The treatment with bisphosphonates can have severe side effects, ranging from gastrointestinal disturbances to osteonecrosis of the jaw [5].

6.2.4 Drug interactions and toxicity

Excess of phosphate can lead to interactions within the human body with calcium, iron and magnesium, and can lead to diarrhoea and may even be toxic. Phosphate and calcium levels are directly connected, and an excess of phosphate will lead to the removal of calcium from the bones and teeth. This will cause osteoporosis and problems with the health of teeth and gums. Athletes often use phosphate supplementation, but a healthcare specialist should monitor this application.

Interactions for phosphate preparations with several over-the-counter and prescription drugs are known. Antacids containing aluminium, calcium and magnesium ions can bind phosphate in the digestive tract and prevent phosphate from being absorbed. This can lead in extreme cases to hypophosphataemia. Potassium-sparing diuretics and potassium supplements in combination with phosphate preparations may lead to elevated levels of blood potassium levels (hyperkalaemia). Hyperkalaemia can be a serious life-threatening problem (see Chapter 2).

6.3 Arsenic

Arsenic is a metalloid of the nitrogen group. Two allotrope forms of elemental arsenic have been reported: yellow arsenic and grey arsenic, the latter being usually the more stable form. Arsenic readily oxidises in air to arsenic trioxide (As_2O_3). Arsenic is mostly found either in its native state or as arsenic sulfide in the form of realgar (As_4S_4) or orpiment (As_2S_3). Arsenic can exist in three different valence states (zerovalent, trivalent and pentavalent). Arsenic forms covalent bonds with carbon, oxygen and hydrogen. The toxicity varies widely and depends on the physical state of the compound and its absorption/elimination rate.

Trivalent arsenics (As(III)) are derivatives of the arsenous acid (H_2AsO_3 – arsenite) and arsenic trioxide (AsO_3). Examples of pentavalent arsenic (As(V)) include derivatives of the arsenic acid (H_3AsO_4 – arsenate).

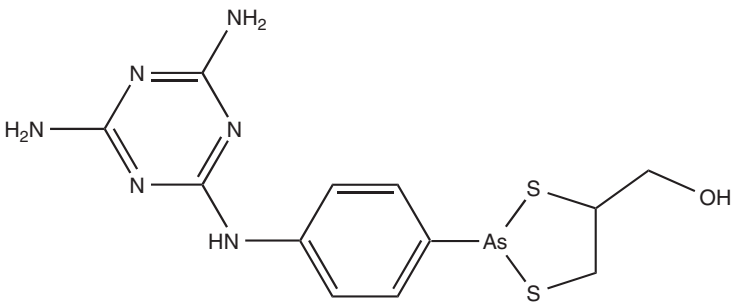

Figure 6.14 *Chemical structure of Melarsoprol*

Organic arsenic-based compounds, that is, compounds containing arsenic–carbon bonds, are usually less toxic than their inorganic counterparts. This is mainly due to their quicker excretion from the human body.

Arsenic is known to be one of the most toxic heavy metals. Compounds containing arsenic have a long history of use as poisons, but they also have a long historical medicinal use. As_2O_3, As_2S_3 (orpiment) and As_2S_2 (realgar) have been used as early as 2000 BC as drugs, for example, to cure cancerous tumours, ulcers and other diseases of the time. Nevertheless, the therapeutic use of arsenic-based compounds continued; for example, Galen (130–200 AD) recommended the application of a paste of arsenic sulfide against ulcers. Paracelsus 'ignored' any kind of formulation and recommended the clinical use of elemental arsenic. Fowler's solution (1% potassium arsenite) was applied in a variety of clinical applications. Interestingly, it was the main treatment option for chronic myelogenous leukaemia (CML) until it was replaced by radiation and chemotherapy in the twentieth century. Again, until the twentieth century, arsenic-based drugs were, for example, mostly used to combat trypanosomal infections. Indeed, Melarsoprol is currently approved for the treatment of late-stage African trypanosomiasis (Figure 6.14).

6.3.1 Salvarsan: the magic bullet – the start of chemotherapy

Salvarsan was a synthetic arsenic-based drug discovered in 1909 by Ehrlich and his team. In 1910, Ehrlich introduced Salvarsan (3-amino-4-hydroxyphenylarsenic), also known as *arsphenamine* or *compound 606*, to the market as a cure for syphilis caused by the bacterium *Treponema pallidum*.

6.3.1.1 Historical developments

Early in his studies, Ehrlich believed in the search for the 'magic bullet' – a treatment that would result in 'the use of drugs to injure an invading organism without injury to the host' [8]. This can be regarded as the start of chemotherapy. Early in his research career, Ehrlich became interested in bacteriology and the use of aniline and other dyes to selectively stain bacteria. In 1904, Ehrlich used trypan red to selectively stain trypanosomas (protozoa responsible for the African sleeping sickness). He discovered that no other cells took up the dye, and he got the idea of selectively targeting single cells from this experiment – the early start to chemotherapy. Ehrlich and his team managed to show that mice infected with trypanosomas could be cured with trypan red, but human experiments failed. Even today, trypan blue as staining agent is used to distinguish between living and dead cells because living cells do not take up the dye [8].

In 1905, the bacterium *T. pallidum* was identified by Schaudinn and Hoffmann as the cause syphilis. This discovery inspired Ehrlich to search for a cure using his targeted approach. 'We must search for magic

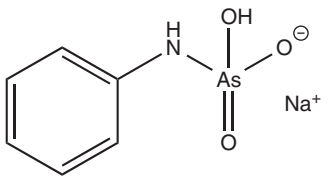

Figure 6.15 *Chemical structure of Atoxyl according to Béchamp*

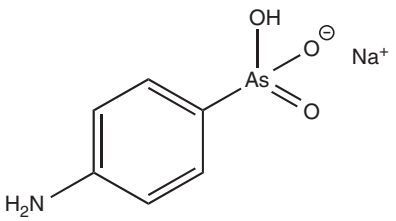

Figure 6.16 *Chemical structure of Atoxyl according to Ehrlich and Bertheim*

bullets' [9], Ehrlich commented during his research. 'We must strike the parasites and the parasites only, if possible, and to do this, we must learn to aim with chemical substances' [9].

Béchamp, teaching medicinal chemistry at the University of Montpellier, synthesised in 1863 a compound from aniline and arsenic acid, which became known later as *Atoxyl*. The name Atoxyl stems from its decreased toxicity. Béchamp characterised his compound as an anilide, and its structure is shown in Figure 6.15 [10].

In 1905, Thomas and Breinl showed that Atoxyl was effective in the treatment of trypanosomas, mainly *Trypanosoma brucei* gambiense – the cause of the African sleeping sickness, which was the main health problem around that time in Africa. Nevertheless, very high doses were required to show any pronounced effect, and as a result severe side effects such as blindness and damage to the optical nerve were common issues [10].

Inspired by this research, Ehrlich hired the chemist Bertheim in 1905. Bertheim revised the structure of Atoxyl and the correct chemical formula was assigned. Atoxyl was identified as an *p*-anilinyl arsenic acid derivative on the basis of its properties to reduce Tollen's reagent $[Ag(NH_3)_2]^+$ to metallic silver and its potential use to synthesise the corresponding diazo dye. Diazotisation is possible only for primary aromatic amines and therefore it could be concluded that Atoxyl had to be an arsenic acid rather than an anilide derivative; the correct structure according to Ehrlich and Bertheim is shown in Figure 6.16 [10].

Ehrlich's coworker, Hata, discovered a way to infect rabbits with *T. pallidum*. No one before had been able to produce syphilis in an animal, and in 1909 the first successful *in vivo* experiments in rabbits were performed. Having identified the correct structure of Atoxyl, Ehrlich and his team were inspired to search for a huge number of derivatives. Eventually, compound 606 was synthesised and introduced as an agent against syphilis. The compound was later marketed as Salvarsan, receiving its name from the Latin word 'salvare', which means to preserve, to heal. In 1909 and 1910, the first human tests on patients with syphilis and relapsing fever were extremely successful, and Salvarsan was marketed from 1910. For the first time, an infectious and fatal disease in humans could be treated with a man-made molecule, and Salvarsan brought Ehrlich world-wide fame (Figure 6.17) [10].

However, Ehrlich and his team did not stop with the discovery of Salvarsan. In particular, formulation issues encouraged them to search for a derivative which was easier to administer in order to make an injectable

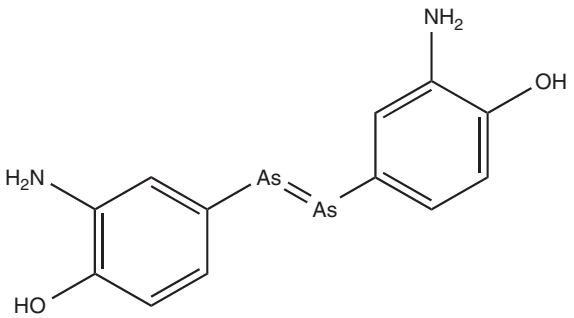

Figure 6.17 *Chemical structure of Salvarsan*

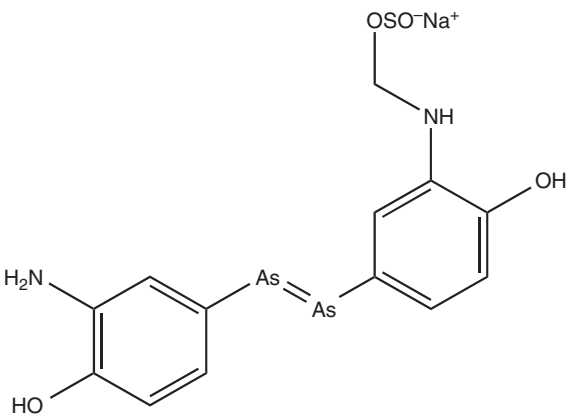

Figure 6.18 *Chemical structure of Neosalvarsan*

solution. Neosalvarsan (compound 914) is a salt derivative of Salvarsan and is water soluble, which showed reduced side effects (Figure 6.18) [10].

Around a decade later, doubts arose about the stability of an As═As double bond, as analysis of the arsenic content of the samples never conformed to the structure stated. Later work showed that neither Salvarsan nor Neosalvarsan was the active pharmaceutical ingredient (API). In 1930, the oxidised compound Oxophenarsine, containing an As═O unit, was identified as the active ingredient and was later marketed under the trade name Mapharsen. Mapharsen was used until the 1940s when it was replaced by Penicillin. Mapharsen was actually synthesised in Ehrlich's laboratory as compound number 5, but it was believed to be too toxic for any clinical application (Figure 6.19) [10].

Generally, the use of arsenic-based drugs has ceased, especially as a result of the development of Penicillin. Nevertheless, Melarsoprol and an arsenic-based drug closely related to Atoxyl are licensed to treat sleeping sickness.

6.3.1.2 Synthesis and structural analysis of Salvarsan

In Ehrlich's time, it was very reasonable to formulate the structure of Salvarsan as he did. But the As═As double bonds are not stable under the reaction conditions chosen by Bertheim and Ehrlich. Their proposed synthetic route was based on the reaction of 3-nitro-4-hydroxyphenyl-arsonic acid with dithionite. As a result,

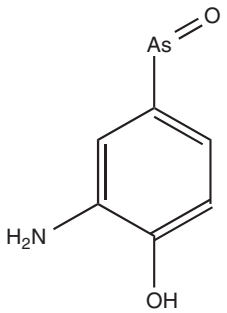

Figure 6.19 *Chemical structure of Mapharsen*

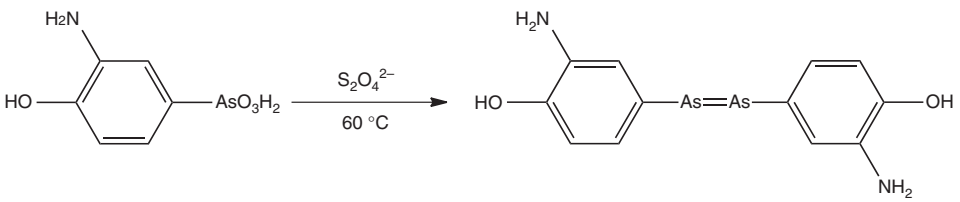

Figure 6.20 *The initial synthesis of Salvarsan according to Ehrlich and Bertheim*

the nitro group is reduced to an amine group and simultaneously As(V) is reduced to As(I), resulting in a compound with the formula 3-H_2N-4-HOC_6H_3As (see Figure 6.20). The product was then isolated as the hydrochloride salt 3-H_2N-4-$HOC_6H_3As{\cdot}HCl{\cdot}H_2O$. Unfortunately, this synthetic route was not always reproducible [11].

Christiansen *et al.* published in 1920 a two-step process leading to the sulfur-free product. The reaction involved the initial reduction of the nitro group with sodium dithionite and the subsequent reduction of the As(V) with hypophosphorous acid (Figure 6.21) [11].

Nevertheless, subsequent research has shown that dimeric arsenic-based structures exist only in sterically crowded molecules. The real structure of Salvarsan is not dimeric. Research published in 2005 by Lloyd *et al.* using different mass spectroscopic techniques showed that Salvarsan in solution consisted of small cyclic species with ring sizes of three and five arsenic atoms (see Figure 6.22). Nevertheless, this final structure of Salvarsan has still not been entirely identified [11].

6.3.2 Arsenic trioxide: a modern anticancer drug?

Arsenic trioxide, often denoted as As_2O_3 but more correctly stated as As_4O_6, is an inorganic compound mainly used as the precursor for organoarsenic compounds. It can be obtained by the oxidation of arsenic-containing minerals in the air, such as roasting of orpiment.

$$2As_2S_3 + 9O_2 \rightarrow As_4O_6 + 6SO_2$$

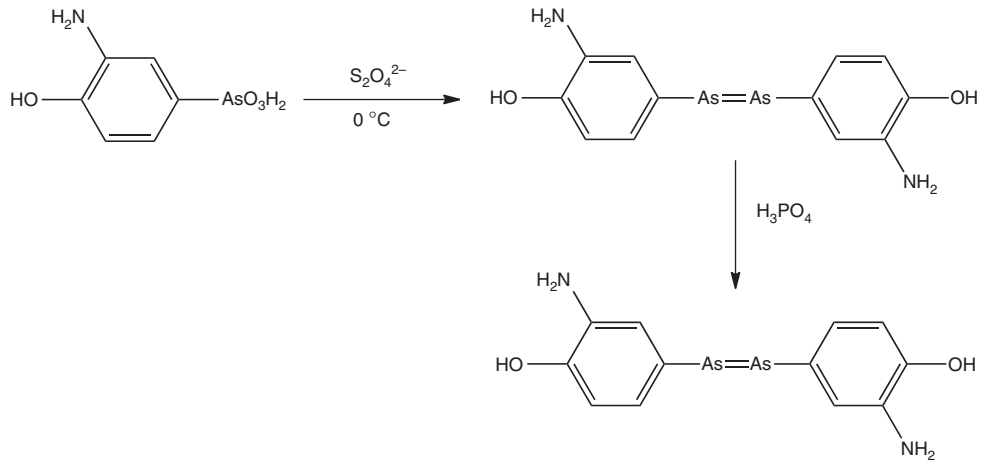

Figure 6.21 *Synthesis of Salvarsan according to Christiansen*

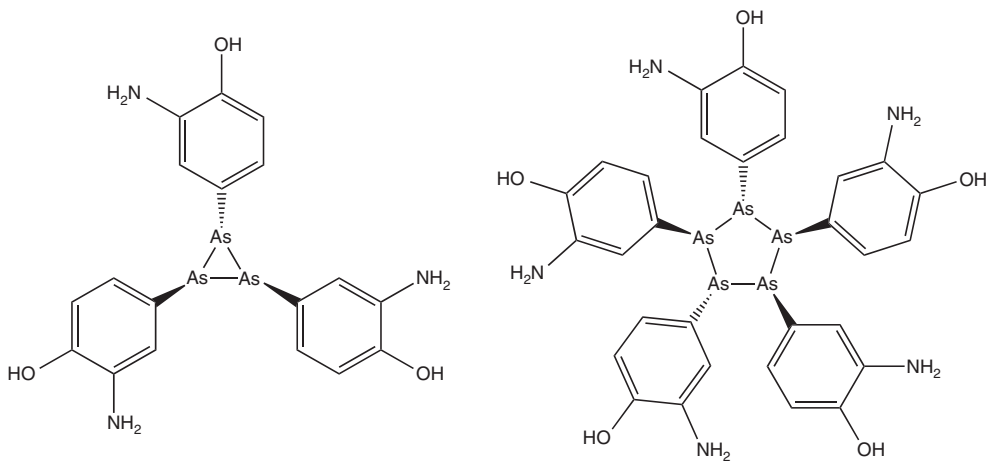

Figure 6.22

As_4O_6 is sparingly soluble in water and is an amphoteric compound. It reacts with alkali with the formation of arsenates, and arsenite trichlorides are synthesised in the presence of an acid.

$$As_4O_6 + 12NaO \rightarrow 4Na_3AsO_3 + 6H_2O$$

$$As_4O_6 + 12HCl \rightarrow 4AsCl_3 + 6H_2O$$

Arsenic trioxide is highly toxic. It is readily absorbed in the digestive system, through inhalation and skin contact. With a half-life of 1–2 days, elimination occurs rapidly at first via a methylation reaction and excretion in the urine. Around 30–40% of arsenic trioxide is incorporated into bones, muscles, hair and nails.

This means that elimination can take months, and any arsenic poisoning is detectable for the same period. Arsenic poisoning is characterised by digestive problems such as vomiting, diarrhoea and abdominal pain, as well as cardiovascular problems. Lower doses can lead to liver and kidney damage as well as changes in the pigmentation of the skin and nails (occurrence of so-called Mees stripes) [12].

Nevertheless, arsenic trioxide is long known for its therapeutic properties especially in the traditional Chinese medicine and homeopathy. In the latter, it is known as *arsenicum album* (dilution of arsenic trioxide). Despite its toxicity, arsenic trioxide and its derivatives have found application in the treatment of cancer. In 1878, Fowler's solution (1% potassium arsenite) showed a reduction of white blood cells when administered to healthy people and patients with leukaemia. It was reported in 1930 that arsenic trioxide was effective in patients with CML. It was used after radiation therapy until modern chemotherapy replaced this treatment approach [12].

Arsenic trioxide – marketed under the trade name Trisenox – gained FDA approval in 2000 for the treatment of acute promyelocytic leukaemia (APL). Trisenox, an injectable formulation, has been licensed for use in patients with induction of remission with APL after all-*trans* retinoic acid (ATRA) and anthracycline chemotherapy, and where APL is characterised by the presence of the t(15;17) translocation or PML/RAR-α (promyelocytic leukemia/retinoic acid receptor-alpha) gene expression. Trisenox was also approved in 2002 by the European Agency for the Evaluation of Medical Products for the treatment of adults with relapsed APL [13].

APL is a subtype of acute myelogenous leukaemia (AML), which is a cancer of the blood and bone marrow. The disease is caused by a chromosomal translocation involving the RAR-α gene and therefore unique compared to other forms of AML in its response to ATRA therapy. Unfortunately, about 20–30% of patients do not achieve remission from the combination of ATRA and cytotoxic chemotherapy, or they relapse. Trisenox was reported to achieve a 70% complete response rate in patients with APL which relapsed after treatment with cytotoxic chemotherapy and ATRA [13].

6.4 Exercises

6.4.1 Oral phosphate preparations contain typically monobasic sodium phosphate, and/or disodium phosphate. Determine the chemical formulae of these three compounds.

6.4.2 Draw the Lewis structure of the following molecules and determine the oxidation state of phosphorus:

(a) H_3PO_4
(b) PCl_3
(c) Na_2HPO_4

6.4.3 Determine the oxidation state of arsenic in the following molecules:

(a) As_2O_3
(b) H_3AsO_4
(c) AsF_5

6.4.4 A typical IV solution for the treatment of hypophosphataemia contains 100 mmol/l phosphate, 19 mmol/l potassium ions and 162 mmol/l sodium ions. Calculate the amount of phosphate, potassium and sodium ions present in 500 ml. Express your answer in grams.

6.5 Case studies

6.5.1 Phosphate solution for rectal use

Your pharmaceutical analysis company has been contacted by an important client and asked to analyse a batch of phosphate solutions for use in enemas. The description of your brief states that you are supposed to analyse the APIs in this solution following standard quality assurance guidelines.

Typical analysis methods used for quality purposes are based on titration reactions. A certain amount of solution is diluted with water. A known amount of this solution is then titrated with sodium hydroxide or hydrochloric acid depending on the API. Phenolphthalein and methyl red solutions are typically used as indicators [14].

(a) Research the APIs typically present in a solution used for enemas and describe their chemical structure. Describe the type of titration suggested. Describe the chemical structure and mode of action of the indicators.
(b) Formulate the relevant chemical equations.
(c) Phosphate enemas typically contain 12.8 g sodium dihydrogen phosphate dihydrate and 10.24 g disodium phosphate dodecahydrate and water made up to a 128 ml solution.

For the determination of the sodium dihydrogen phosphate dehydrate content, 20 ml of this solution is diluted with 80 ml of water and titrated with 0.5 M sodium hydroxide solution using phenolphthalein as indicator. The following amounts of sodium hydroxide are used:

25.0 ml	25.6 ml	25.4 ml

For the determination of the disodium hydrogen phosphate dodecahydrate content, 50 ml of this solution is titrated with 0.5 M hydrochloric acid using methyl red as indicator. The following amounts of hydrochloric acid are used:

22.0 ml	22.3 ml	22.4 ml

Calculate the amount of sodium dihydrogen phosphate and disodium hydrogen phosphate 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.

6.5.2 Forensic test for arsenic

Arsenic compounds are known for their toxicity and are often used in poisons. In order to obtain forensic evidence, specific tests were developed for the qualitative analysis of arsenic-based compounds. The so-called Marsh test was published in 1836 and is based on the reduction of As^{3+} in the presence of Zn.

(a) Research the conditions needed for the Marsh test.
(b) Formulate the relevant reduction and oxidation equations.
(c) Is it possible to use the Marsh test as a quantitative test?

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