5

The Carbon Group

Members of group 14 of the periodic table (14th vertical column) are summarised as carbon group consisting of carbon (C), silicon (Si), germanium (Ge), tin (Sn) and lead (Pb) (Figure 5.1).

Group 14 elements have four valence shell electrons and therefore tend to form covalent compounds. Nevertheless, with increasing mass and atomic radius, the elements show increasingly more metallic characteristics and have lower melting and boiling points. Elements within this group show a graduation from nonmetallic elements (C) to elements that are classified as metals (Pb). Silicon is generally seen as nonmetallic, whereas germanium is metallic. Nevertheless, this classification is not definite. Silicon and germanium both form covalent diamond-type structures in the solid state, but their electrical behaviour indicates more a metallic behaviour. Therefore, silicon and germanium are classified as metalloids (see Chapter 4).

Carbon is the essential element to life on earth, and the chemistry related to carbon is classified as organic chemistry and we will therefore not discuss it any further in this book. Organometallic chemistry relates to the interaction of carbon compounds with metals, and the basic concepts will be discussed in Chapter 8.

Tin and lead have been under investigation for use as anticancer and antimicrobial agents, but so far with limited success. This chapter will discuss the pharmaceutical applications of silicon- and germanium-based drugs.

5.1 General chemistry of group 14 elements

5.1.1 Occurrence, extraction and use of group 14 elements

Silicon is, after oxygen, the second most abundant element in the earth's crust. It occurs in a range of minerals and sand (SiO_2, quartz). In contrast, germanium, tin and lead are relatively rare elements, with tin and lead being extracted for thousands of years from their ores. The main source for tin is cassiterite (SnO_2) and for lead galena (PbS). Germanium was first isolated from the mineral argyrodite when it was discovered, but there are no major deposits of this mineral. Germanium is nowadays mainly sourced from zinc and copper ores.

Silicon can be extracted from silicates or sand by reducing SiO_2 with coke at high temperatures at around 3000 °C.

$$SiO_2 + 2C \rightarrow Si + 2CO \tag{5.1}$$

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

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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 5.1 *Periodic table of elements; group 14 elements are highlighted*

Germanium is extracted from zinc ores in a very complicated process as it has aqueous properties similar to those of zinc. Once the germanium/zinc mixture has been sufficiently enriched with germanium, it is heated in HCl with Cl_2 in order to allow the formation of germanium tetrachloride ($GeCl_4$). $GeCl_4$ can be easily separated from $ZnCl_2$ because the former has a significantly lower boiling point, and after hydrolysis germanium dioxide (GeO_2) is obtained. GeO_2 can be reduced to elemental Ge in a stream of hydrogen gas. Elemental Sn is extracted from the ore cassiterite (SnO_2) via reduction with carbon. Lead is obtained from its sulfide (PbS, galena), which is first roasted in the presence of oxygen and then reduced with carbon to give elemental Pb.

$$PbS + 1^1/_2O_2 \rightarrow PbO + SO_2$$

$$PbO + C \rightarrow Pb + CO$$

Silicon is used in a wide variety of applications. In nature, silicon does not exist as the pure metal and most commonly occurs in silica (including sand) and silicates. Silicon dioxide, also known as *silica*, is a hard substance with a high melting temperature and clearly very different from carbon dioxide. Molten silica can be used to make glass, an extremely useful material, which is resistant to attack by most chemicals except fluorine, hydrofluoric acid and strong alkalis. Silicon atoms can also be found in the class of compounds called *silicones*. Silicones are inert synthetic polymers with a wide range of uses including as sealants, cookware, adhesives and medical applications. Silicones contain next to silicon atoms also carbon, hydrogen and oxygen atoms (Figure 5.2).

Pure silicon metal is used in semiconductors, the basis of all electronic devices, and is most well known for its application in solar panels and computer chips. Germanium can be mainly found not only in electrical components and in semiconductors but also in some optical applications and some specialised alloys.

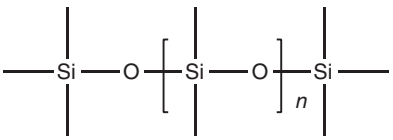


Figure 5.2 *Structure of silicones*

*A **semiconductor** is a crystalline solid that has an electric conductivity between that of a conductor (e.g. copper) and an insulator (e.g. glass). This effect can be a result of impurities or temperature.*

Metallic tin has many applications, but the most well known one is the use as lining for drink and food cans. It is also used in alloys – bronze is an alloy of copper and tin – and organotin compounds find their application in poly(vinyl chloride) (PVC) plastics. Tin is often referred to as a *poor metal* and it has two allotropes: grey tin and white tin.

Lead is a grey metal and most lead is used in batteries. Other major uses, such as in plumbing or as antiknock agent in petrol (tetraethyl lead, $Pb(C_2H_5)_4$), have declined over recent years because of the high toxicity of lead. Pb is a neurotoxin when ingested and many lead compounds are water soluble. Therefore, water lines have been replaced by specialised plastic material, and in most industrialised countries only unleaded petrol is sold.

5.1.2 Oxidation states and ionisation energies

Group 14 elements can have the oxidation state +2 or +4, with the latter one being the dominant one. The stability of the oxidation state +2 increases for elements further down the group, such as Sn and Pb. Group 14 elements have four valence electrons, two in the s orbital and two in the p orbital. Therefore, the first four ionisation energies increase evenly, whereas there is a significant increase to the fifth (Table 5.1).

5.1.3 Typical compounds of group 14 elements

The chemistry of group 14 elements is different from that of its naming element, carbon. The best example is the ability of carbon to form double and triple bonds. None of the remaining group 14 elements shows the same behaviour and there are only very few compounds known that contain silicon–silicon double and triple bonds. Carbon forms double and triple bonds through the overlap of its 2p orbitals. In contrast, the overlap of the 3p orbitals in silicon is weaker, and as a result silicon does not form multiple bonds as readily as carbon.

5.1.3.1 Oxides

Silicon oxides can be very complex structures, which is in contrast to the simple linear molecule carbon dioxide with its C═O bonds. The most basic molecule is SiO_2 (silica), which is an extended array of SiO_4 units where the oxygen atoms bridge the neighbouring silicon atoms. Silicon forms an array of oxides that occur in many minerals. All those are made up of SiO_4 tetrahedra forming rings or chains with an overall

Table 5.1 *Ionisation energy (kJ/mol) for group 14 elements [1]*

	First	Second	Third	Fourth	Fifth
C	1 086	2 352	4 620	6 222	37 827
Si	787	1 577	3 231	4 356	16 091
Ge	762	1 537	3 302	4 410	9 020
Sn	709	1 412	2 943	3 930	6 974
Pb	716	1 450	3 082	4 083	6 640

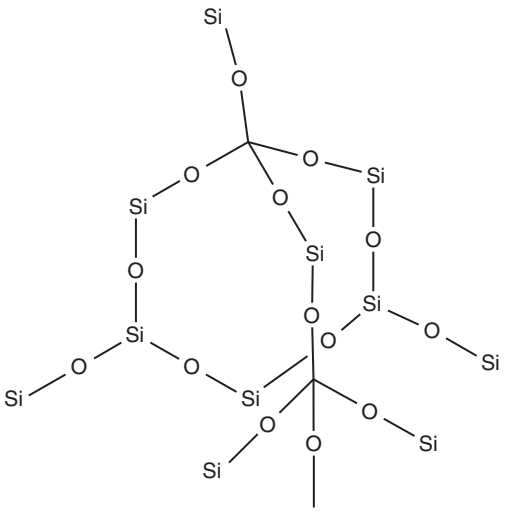


Figure 5.3 *Chemical structure of SiO_2*

negative charge. The negative charges are balanced by metal ions (e.g. alkali and alkaline earth metals). One of the best known examples is the commercially available synthetic zeolite, which is an aluminosilicate incorporating aluminium ions. Zeolite is used as an absorbent and in the production of laundry products (Figure 5.3).

Germanium dioxide has the chemical formula GeO_2 and forms as a passivation layer on pure germanium when the semi-metal is in contact with atmospheric oxygen. GeO_2 forms structures that are similar to SiO_2 depending on the reaction conditions. Germanium monoxide (GeO) is formed when GeO_2 is heated with powdered germanium at 1000 °C. GeO_2 is used in optical devices such as lenses and optical fibres, amongst other applications.

5.1.3.2 Hydrides

Silicon hydrides are called *silanes* and are structurally similar to their carbon analogues, with the general formula Si_nH_{2n+2}. Silanes are typically colourless and can be gases or volatile oils. Germanium hydrides are accordingly called *germanes* and these are generally less reactive than silanes. A classic example is SiH_4, which ignites spontaneously in air whereas GeH_4 is stable. Tin hydrides (SnH_4), called *stannanes*, are less stable and decompose slowly in air to tin and hydrogen gas. PbH_4 has not been isolated or prepared so far, and only hydrides containing organic substituents have been observed.

5.1.3.3 Halides

Group 14 elements generally form MX_4-type compounds, but germanium, tin and lead also form compounds of the type MX_2. Tetrachlorides of silicon and germanium are important precursors and are used in the synthesis of ultrapure silicon and germanium. These find applications in the electronic industry as materials for semiconductors. Silicon tetrachloride instantly hydrolyses when it comes into contact with water.

5.2 Silicon-based drugs versus carbon-based analogues

Silicon chemistry has been of interest as a source for the design of novel pharmaceutically active compounds. Why is it possible to introduce a silicon group or replace a carbon centre by silicon and what are the resulting changes? Carbon and silicon are both group 14 elements exhibiting similarities and differences:

Valency: Silicon and carbon both possess four valence electrons as they show an analogous electron configuration (C: [He]$2s^2 2p^2$; Si: [Ne]$3s^2 3p^2$).

Coordination number: Unlike that of carbon, the chemistry of silicon is influenced by the availability of its 3d orbitals to be involved in additional bonding interactions. Silicon is therefore capable of increasing its coordination number from 4 to 6 and thus forming isolatable penta- and hexacoordinated silicon-based compounds. Nevertheless, for silicon a coordination number of 4 (sp^3 hybridisation) is favoured especially over coordination numbers 2 (sp hybridisation) and 3 (sp^2 hybridisation). Consequently, the formation of double and triple bonds is disfavoured in contrast to carbon-based reaction centres.

Bond length: Silicon has a larger covalent radius than carbon, resulting in the formation of longer bonds than carbon–carbon bonds (typical C—C bond length = 1.54 Å), silicon–silicon bonds (typical Si—Si bond length = 2.33 Å) and silicon–carbon bonds (typical Si—C bond length = 1.89 Å). As a result, silicon-containing compounds show higher conformational flexibility and therefore steric arrangements different from analogous carbon-based compounds. Differences in interaction with proteins and consequently alterations of pharmacodynamics and pharmacological profiles have been observed.

Electronegativity: Silicon is more positive than the neighbouring carbon (electronegativity according to Pauling: Si = 1.90, C = 2.55), resulting in different bond polarisation of analogous carbon–element and silicon–element bonds. As a result, chemical reactivity and bond strength can differ significantly. This can provide improved or altered potency if carbon moieties are switched to silicon-based ones within pharmacophores, especially if hydrogen bonding is involved in the mode of action (Figure 5.4).

Lipophilicity: In general, silicon-based compounds demonstrate an enhanced lipophilicity in comparison to their carbon-analogous due to their different covalent radii. This provides an interesting opportunity for exploitable pharmacokinetic potential in drug design, for example, for drugs that are prone to hepatic metabolism. Silicon-based compounds involved in hepatic metabolism have been observed to exhibit an increased half-life when compared to their carbon analogues. Increased lipophilicity is also believed to be useful in the design of drugs that are supposed to cross the blood–brain barrier. Therefore silicon analogues with their increased lipophilicity can be very interesting drug candidates.

Currently, there are only a small number of silicon-containing compounds under investigation for pharmaceutical use. Silicones are the only silicon-based compounds widely used in medicine. These oligosiloxanes

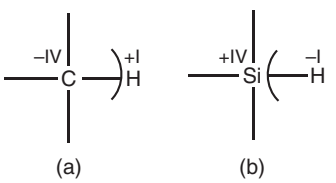


Figure 5.4 *(a) C—H and (b) Si—H bond polarisation*

and polysiloxanes have no carbon analogues and they are widely used for plastics, implants, catheters and many other applications.

The limitations of novel organosilicon compounds are very often attributed to insufficient funding and poor evidence of demonstrated efficacy. There is also an on-going debate about the toxicity of silicon-based therapeutics. So far, no increased systematic toxicity of silicon-containing compounds in comparison to their carbon-analogous has been detected.

Nevertheless, several organosilicon compounds have made it to clinical trials. In the following sections, a couple of interesting examples ranging from steroids being used by bodybuilders to anticancer and antispastic drugs under development are presented.

5.2.1 Introduction of silicon groups

A convenient method to introduce a silicon group is through the so-called silylation. A hydrogen atom that is bonded to a heteroatom (sulfur, nitrogen or oxygen) is exchanged by a silyl group (see Figure 5.5).

Carbon silylation, that is, the introduction of a silicon group next to a carbon centre, is also used for the design of novel drugs. This approach potentially allows changing the properties of the novel drug candidate significantly. It can lead to enhanced blood stability, increased cell penetration and altered pharmacokinetics. Several compounds have entered clinical trials, including the muscle relaxant silperisone (Figure 5.6) [1].

5.2.1.1 Silabolin

The anabolic compound silabolin is an example of a drug in which this silylation approach has been used. Silabolin is an injectable steroid containing a trimethylsilyl group, and was and still is used as an anabolic preparation by bodybuilders. It is known to have a relatively low androgenic activity like the natural anabolic hormone testosterone. Silabolin was officially registered in the (former) USSR as a domestic anabolic drug. It is believed to influence the protein synthesis in humans. Silabolin itself is a white powder, which is sparingly soluble in ethanol but not soluble in water [2]. Its propensity to cause heart and liver defects is under discussion and its effectiveness is being critically discussed amongst bodybuilders (Figure 5.7) [1].

5.2.1.2 Silperisone

Tolperisone is a centrally acting muscle relaxant used, for example, in the treatment of acute muscle spasms in back pain. Previous *in vitro* and *in vivo* studies in mice have demonstrated that silperisone may have the potential to reduce both central nervous system depressing and motor side effects. Phase I clinical trials were

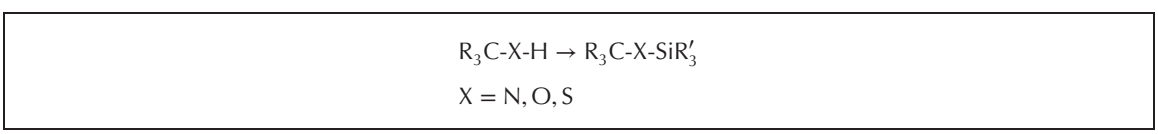


Figure 5.5 *Silylation reaction*

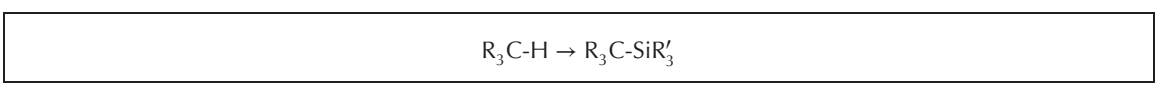


Figure 5.6 *Example for carbon silylation reaction*

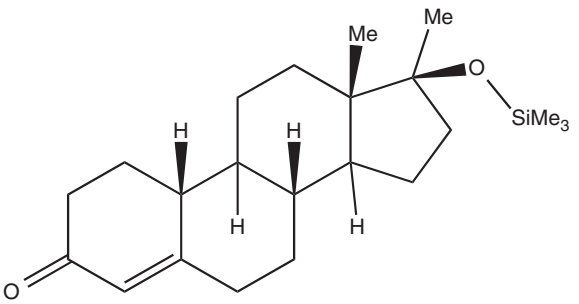


Figure 5.7 *Chemical structure of silabolin*

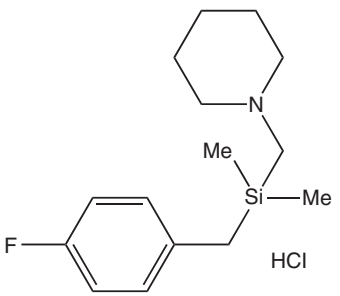


Figure 5.8 *Chemical structure of silperisone*

conducted with doses up to 150 mg/day. No adverse side effects were detected, and the observed plasma levels were deemed to be effective in preclinical trials. Nevertheless, chronic toxicities were observed in animal studies and the research was discontinued (Figure 5.8) [3].

5.2.1.3 Indomethacin

Indomethacin (see Figure 5.9) is a nonsteroidal anti-inflammatory agent used in pain and moderate to severe inflammation in rheumatic diseases and other musculoskeletal disorders. It is a COX (cyclooxygenase) inhibitor and therefore interrupts the production of prostaglandins [4].

A series of new silicon compounds, based on the structure of indomethacin, have been synthesised and are under investigation as novel anticancer agents. The carboxyl group of indomethacin was reacted with a series of amino-functionalised silanes. The resulting products have been shown to be significantly more lipophilic and more selective to COX-2. Furthermore, *in vitro* testing has shown an increased uptake of the new compounds at the tumour site. The silane-functionalised indomethacin derivatives exhibited a 15-fold increased antiproliferative effect when tested against pancreatic cancer (Figure 5.10) [5].

5.2.2 Silicon isosters

The carbon/silicon switch strategy, meaning the replacement of carbon centres by analogous silicon groups in known biologically active reagents, is currently mainly used for the development of novel silicon-based drug candidates [6].

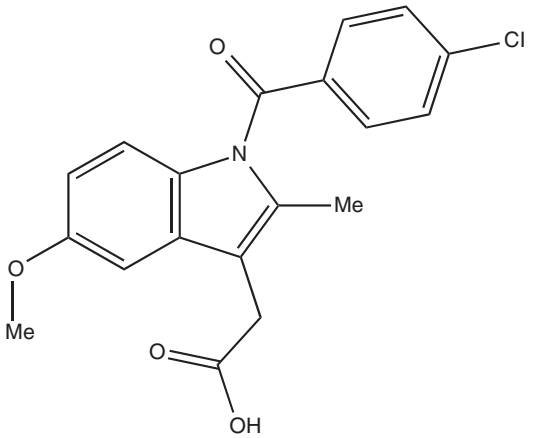


Figure 5.9 *Chemical structure of indomethacin*

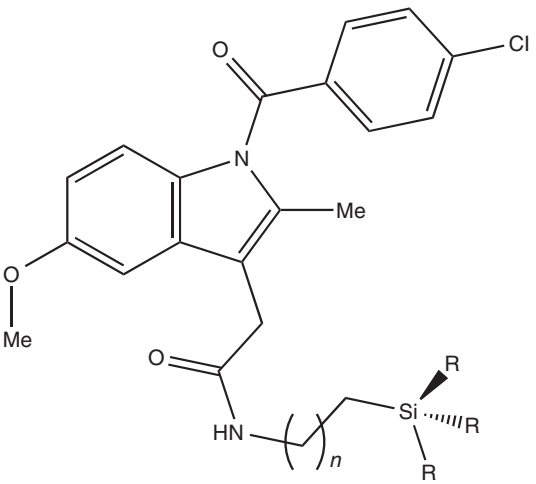


Figure 5.10 *Chemical structure of silicon analogue of indomethacin*

The idea is that the new silicon-based drug candidates have the same chemical structure, with one carbon atom exchanged by a silicon one. The resulting physiochemical changes include, amongst others, altered bond length and changes in the lipophilicity. These alterations can have a significant effect on the biological activity of these novel silicon-based compounds. A variety of these compounds have been synthesised and tested [1]; two examples are presented in the following:

5.2.2.1 Sila-haloperidol

Haloperidol is an analogue of the dopamine D_2 receptor antagonist and is an older antipsychotic drug. The drug is used in the treatment of schizophrenia, a neuropsychiatric disorder. Schizophrenia is characterised by symptoms such as hallucinations, delusions and disorganised speech. It is believed that schizophrenia is

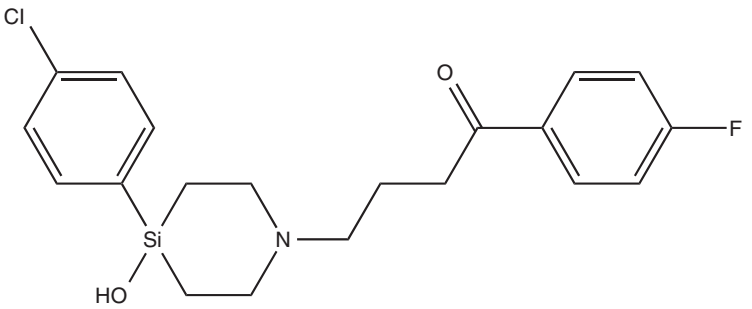


Figure 5.11 *Chemical structures of sila-haloperidol*

caused by problems involving the dopamine regulation in the brain. In general, antipsychotic drugs work by blocking the dopamine D_2 receptors [7].

Haloperidol is such an antipsychotic drug, which was developed in the 1950s and entered the clinic soon after that. Its use is limited by the high incidence of extrapyramidal symptoms (movement disorders caused by drugs affecting the extrapyramidal system, a neural network which is part of the motor system) [8]. Nevertheless, haloperidol may be used for the rapid control of hyperactive psychotic states and is popular for treating restlessness in the elderly.

The silicon analogue, sila-haloperidol, has been synthesised by a sila-substitution of the quaternary R_3COH carbon atom of the 4-hydroxy-4-(4-chlorophenyl)piperidin-1-yl group of haloperidol (see Figure 5.11). Chemical analyses have shown that haloperidol and sila-haloperidol both exist as two analogous conformers but with a different conformer ratio for the carbon and silicon analogues. Biological studies have also shown large differences between the metabolic pathways of the silicon and carbon analogues. Radiolabelling studies have shown similar potencies of the silicon and the carbon compounds at the human dopamine hD_1, hD_4 and hD_5 receptors. Sila-haloperidol was significantly more potent with the hD_2 receptor, thus giving hope to improved side effects related to the metabolism [9].

5.2.2.2 Sila-venlafaxine

Venlafaxine is a serotonin and noradrenalin reuptake inhibitor (SNRI) and is used as an antidepressant. Compared to tricyclic antidepressants, it lacks the antimuscarinic and sedative side effects. Nevertheless, treatment with venlafaxine can lead to a higher risk of withdrawal symptoms [8].

The silicon analogue, *rac*-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-1-silacyclohexan-1-ol, has been synthesised and tested for its biological properties. The hydrochloride salts were examined for their efficacy in reuptake inhibition assays for serotonin, noradrenalin and dopamine. It was concluded that the carbon–silicon switch changed the pharmacological profile significantly in regard to the reuptake inhibition depending on the stereoisomer. (*R*)-Sila-venlafaxine was found to be consistent with selective reuptake inhibition at the noradrenaline inhibitor (Figure 5.12) [10].

5.2.3 Organosilicon drugs

There are several classes of silicon compounds with a clinical use or a proposed biological activity that have no apparent carbon analogues. These compounds use the properties specific to silicon, mainly its ability to form molecules with a penta- and hex-acoordinated silicon centre.

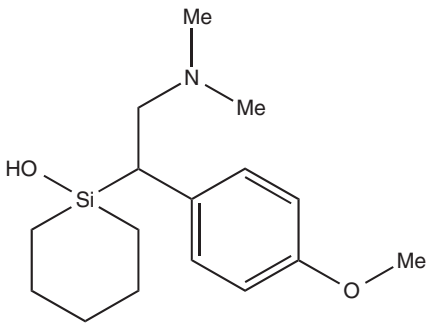


Figure 5.12 *Chemical structure of sila-venlafaxine*

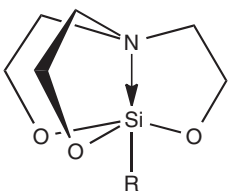


Figure 5.13 *Chemical structure of silatrane*

Silatranes are silicon compounds in which the central silicon atom is pentacoordinated. Silatranes can be highly toxic depending on the organic rest at the silicon centre. Aryl [11] and 2-thienyl-substituted silatranes [12] have been proposed as rodenticides [1]. These compounds are known for their self-detoxification, resulting in a low hazard for dermal toxicity or long-lasting secondary risk of poisoning (Figure 5.13) [13].

Silatranes substituted with alkyl, alkenyl and other groups are significant less toxic and are under evaluation for a variety of biological or clinical applications ranging from the stimulation of collagen biosynthesis to the proposed use as anticancer agents [1].

Silicones (oligo and polysiloxanes, see Section 5.1.1) are the most widely used class of silicon-based compounds clinically. Silicones can be found in plastics, lubricants, catheters, implants and a variety of other medically used items. Silicone fluids, such as simethicone, are known for their antifoaming properties. Simethicone is an orally administered suspension containing polysiloxanes and silicon dioxide. It is an antifoaming agent and is used to reduce bloating by decreasing the surface tension in bubbles. Excessive formation of gas bubbles in the stomach and intestines can be painful and can also be of hindrance for any ultrasound examination. Simethicone can be found in antacids and in suspensions given to babies against colic.

5.3 Organogermanium compounds: balancing act between an anticancer drug and a herbal supplement

The first organogermanium compound, tetraethylgermane, was synthesised by Winkler *et al.* in 1887, but then it took until the middle of the twentieth century for such compounds to be widely synthesised and examined (Figure 5.14).

The major uses for germanium compounds include their application as optical materials (60%) and semiconductors (10%), as catalysts or in chemotherapy. Some Chinese herbs and vegetables contain a relatively

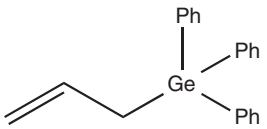


Figure 5.14 *Example for an organogermanium compound*

high amount of germanium, for example, ginseng, oats, soya beans and shiitake mushroom. The germanium is presented in organic form with Ge—O bonds being formed [1].

Germanium dioxide is the oxide of germanium, an inorganic compound, featuring the chemical formula GeO_2. It is formed as a passivation layer on pure germanium after exposure to oxygen. Germanium dioxide generally has a low toxicity, but shows severe nephrotoxicity at higher doses. Germanium dioxide is still offered on the market in some questionable miracle therapies. Exposure to high doses of germanium dioxide can lead to germanium poisoning [1].

In the 1970s, a range of organogermanium compounds were widely marketed as health supplements and became popular because of the therapeutic value of germanium. This encouraged a wide range of research looking into the biological potential of organogermanium compounds. Organogermanium compounds are generally well absorbed after ingestion. Nowadays, mainly compounds with antitumour, immune-stimulating, interferon-reducing and radioprotective properties are being researched. A range of germanium compounds, including germanium sesquioxide, spirogermanium, germatranes, decaphenylgermanocenes, germanium(IV) porphyrins and germyl-substituted heterocycles, have been synthesised and evaluated for their biological activities. Most intensively investigated for a therapeutical application so far have been germanium sesquioxide and spirogermanium (Figure 5.15) [1].

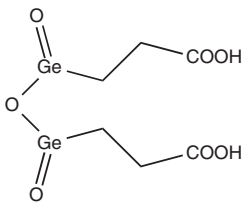
5.3.1 Germanium sesquioxide

2-Carboxyethylgermanium sesquioxide (Ge-132) was investigated in the 1990s to protect the human body from radiation, enrich the oxygen supply, remove heavy metals and scavenge free radicals. Japanese researchers have shown that Ge-132 has a variety of biological activities and could be effective in the treatment of several diseases such as cancer, arthritis and osteoporosis [1].

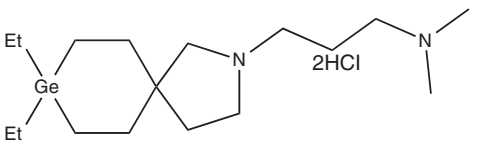
Ge-132 is a white crystalline powder, which is insoluble in organic solvents and soluble in water when heated. The compound does not melt but decomposes at high temperatures above 320 °C. These properties can be explained by the three-dimensional structure of the Ge-132, which consists of Ge_6O_6 rings. The structure is described as an infinite sheet structure. The carboxylate chains form hydrogen bonds between neighbouring chains and hold these germanium sesquioxide sheets together.

Synthesis starts with the generation of organogermanium trichloride, which can be hydrolysed in several steps to form germanium sesquioxide. Organogermanium trichloride itself can be synthesised by reducing germanium dioxide, a toxic starting material, with sodium hypophosphite. This reaction proceeds via a redox reaction, where sodium hypophosphite is oxidised (oxidation state +1 to +2) whilst GeO_2 is reduced (oxidation state +4 to +2). The resulting trichlorogermane is known to be highly unstable [14] and is therefore reacted *in situ* to the relevant organic germanium trichloride via a so-called hydrogermylation reaction (Figure 5.16) [15].

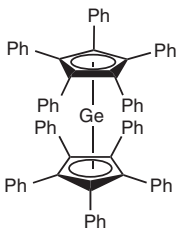
Germanium sesquioxides are generally not known to be embriotoxic, teratogenic, mutagenic or antigenic. Administration over a short term did not reveal any significant adverse effects. Ge-132 contains relatively stable Ge—C bonds, which prevents its fast hydrolysis to the toxic inorganic compound GeO_2. Ge-132 has good water solubility and is excreted from the human body within 24 h. Side effects are mainly due to impurities of



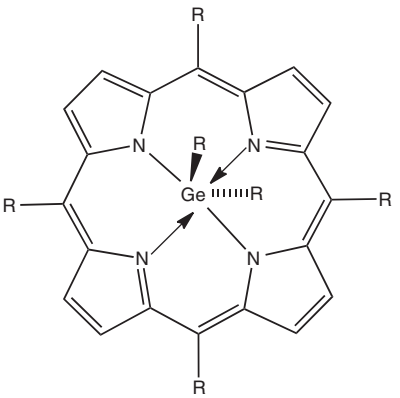
Germanium sesquioxide
(a)



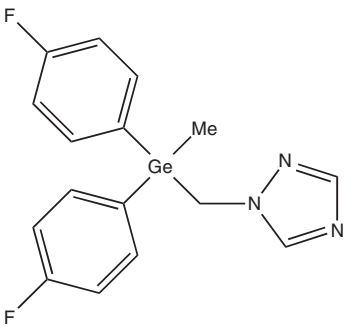
Spirogermanium
(b)



Decaphenylgermanocene
(c)



Germanium (iv) porphyrin
(d)



Germyl-substituted heterocycles
(e)

Figure 5.15 *Chemical structures for germanium compounds investigated for their biological activity. (a) Germanium sesquioxide. (b) Spirogermanium. (c) Decaphenylgermanocene. (d) Germanium(IV) porphyrin. (e) Germyl-substituted heterocycles*

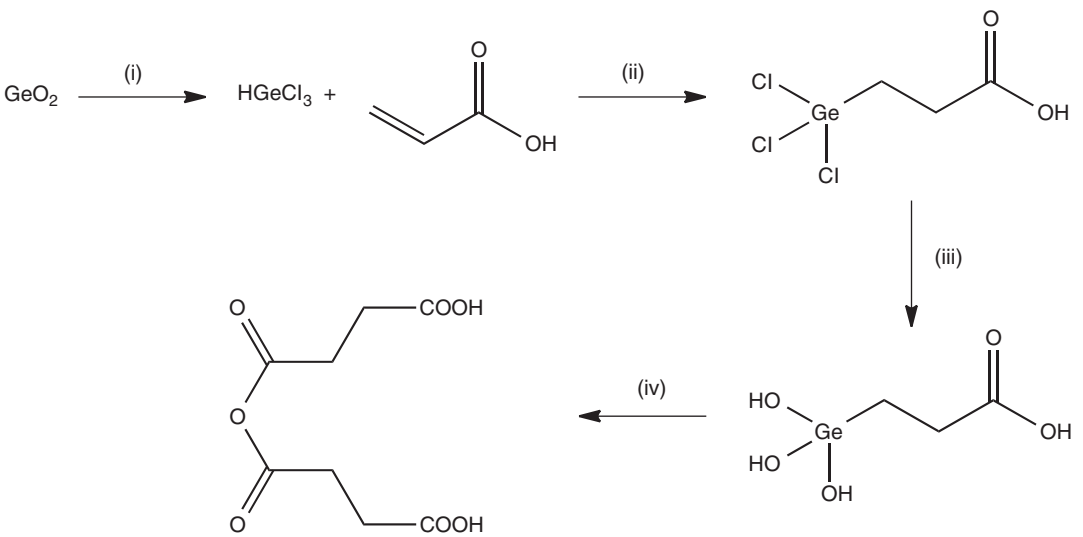


Figure 5.16 *Synthesis of germanium sesquioxide: (i) $Na_2H_2PO_2{\cdot}H_2O$, concentrated HCl, reflux 80°C, 3.5 h, then 0°C; (ii) rt, 24 h 87%; (iii) H_2O, 62% and (iv) hydrolysis*

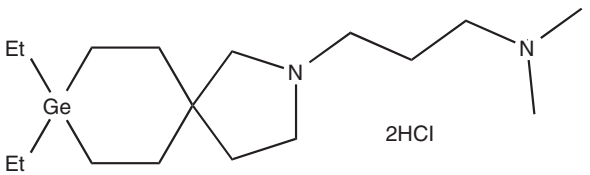


Figure 5.17 *Chemical structure of spirogermanium*

the pharmaceutical product with GeO_2, which can induce renal damage and accumulate in the kidneys, liver and spleen [16].

Lately, the antitumour activity of Ge-132 has been studied. It has been revealed that it possesses antitumour and immune-modulating activity. The first anticancer activity was reported when tested on Ehrlich Ascites tumour. Furthermore, studies were carried out on Lewis lung carcinoma and other cancer types. Oral treatment of pulmonary spindle cell carcinoma with Ge-132 showed complete remission of the cancer [1].

Interestingly, no cytotoxicity was proven when the studies were carried out *in vitro*, and it was concluded that the mechanism works via a stimulation of the host-mediated immunopotentiating mechanism. Nevertheless, the precise mechanism of the anticancer activity of Ge-132 is still not fully understood.

Ge-132 has been scrutinised for a range of biological activities, and studies suggest that the germanium compound may also exhibit antiviral, cardiovascular, antiosteoprotic and antioxidant activities [1, 15b, 17]. For example, studies have shown that Ge-132 is able to avert the decrease in bone strength and loss of bone mineral resulting from osteoporosis [17].

5.3.2 Spirogermanium

2-(3-Dimethylaminopropyl)-8,8-diethyl-2-aza-8-germaspiro[4,5]decane (spirogermanium) was the first organogermanium compound tested as an anticancer agent on a wide variety of human cancer cell lines, such as ovarian, cervix, breast, renal cell cancers and others. Preclinical toxicological evaluation in white mice confirmed the lack of bone marrow toxicity [18].

Spirogermanium entered clinical trials and showed good drug tolerance in phase I clinical trials. Phase II clinical trials revealed consistent neurotoxicity as well as pulmonary toxicities and only moderate activity against ovarian cancer. The mode of action involved is believed to be based on the inhibition of protein synthesis and a secondary suppression of RNA and DNA synthesis (Figure 5.17) [19].

5.4 Exercises

5.4.1 Draw the Lewis structures of the following silicon compounds and compare them with their carbon analogues.

(a) Silicon dioxide
(b) Silicon tetrachloride
(c) Silane
(d) Trichlorosilane

5.4.2 Calculate the ΔEN for all bonds in the following silicon compounds and compare these values with the corresponding carbon bonds.

(a) Silicon tetrachloride
(b) Silane
(c) Trichlorosilane

5.4.3 Research and calculate the bond length in the following compounds and compare them with their carbon analogues.

(a) Silane
(b) Germane
(c) Germanium tetrachloride
(d) Silicon tetrachloride
(e) Silicon dioxide

5.5 Cases studies

5.5.1 Simethicone

Simethicone is a silicon-based antifoaming agent that can be found in a variety of formulations.

(a) Describe the chemical structure of simethicone.
(b) Research its mode of action and route through the human body.
(c) Identify clinical applications for simethicone.
(d) Typical oral suspension used for infants contain simethicone 40 mg/ml. Calculate the weight/volume percentage (%w/v).

5.5.2 Germanium supplements

Organic germanium is sold as a dietary supplement and contains mainly bis-carboxyethyl germanium sesquioxide. Despite many positive health claims, several severe side effects including kidney failure have been reported. These side effects are often explained by toxic impurities, and therefore information on the testing procedures can often be found on the packaging. Typical information would read as follows: 'Analysis performed includes identification by infrared spectroscopy and solubility testing. The purity has been identified by acid group titration and the absence of inorganic germanium has been confirmed by a colour limit test'.

(a) Draw the chemical structure of bis-carboxyethyl germanium sesquioxide.
(b) What is the toxic impurity typically found in these preparations?
(c) What is the solubility of bis-carboxyethyl germanium sesquioxide?
(d) Describe the results you would expect from the infrared analysis.
(e) Research a method for the acid base titration mentioned.
(f) Research the colour limit test for inorganic germanium.

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