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The chemistry and metallurgy of beryllium

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Introduction

Beryllium (Be), the first of the group 2 alkali-earth elements, is a silver-gray metal possessing an unmatched combination of physical and mechanical properties, which are vital for a variety of applications that offer tremendous benefits to society. It is the lightest workable metal, only two-thirds the weight of aluminium, yet it has six times the stiffness of steel, making it an ideal material for stiffness-dependent and weight-limited applications. The chart in Fig. 1 illustrates how much beryllium outclasses other engineering materials with respect to thermal conductivity and dimensional stability (ability of a material to retain its uniformity under stress measured as the Young's modulus to density ratio). These unique properties of beryllium translate into performance enhancement in the end product, for instance the James Webb Space Telescope (JWST: see Fig. 2). The next generation James Webb Space Telescope, scheduled to be launched in 2018 as NASA's replacement for the Hubble telescope, will utilise a 6.5 meter wide beryllium mirror to reveal images of distant galaxies 200 times beyond what has ever been sighted.

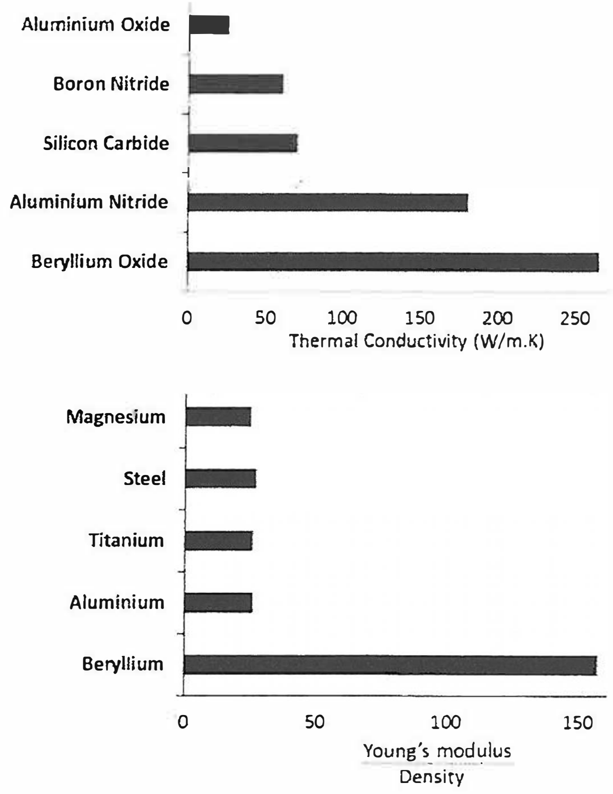


Fig. 1. Some properties of beryllium and beryllium oxide as compared with alternatives (thermal conductivities used with permission from American Beryllia Inc.)

Unfortunately, beryllium is also problematic. It is brittle, hard to machine, expensive and extremely toxic. It is a suspected human carcinogen, an initiator of chronic beryllium disease (CBD) and is regarded as the most toxic non-radioactive element in the periodic table. Surprisingly, this has not deterred its production and usage, making it imperative to gain a better understanding of this element. This review surveys aspects of beryllium metallurgy within a New Zealand context, including applications and toxicity. The coordination chemistry of beryllium is also discussed with an emphasis on the trends amongst ligands that exhibit strong interactions with beryllium as well as research activities within our group to identify suitable chelators for beryllium.

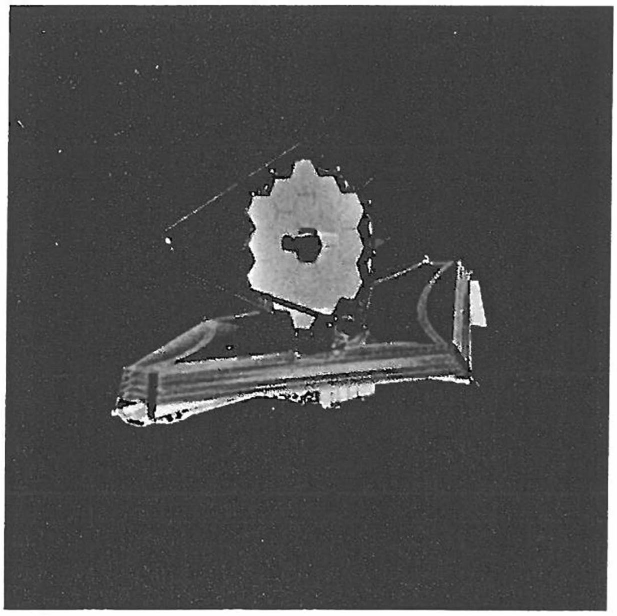


Fig. 2. The James Webb Space Telescope scheduled to be launched in 2018 will utilise a 6.5 m (21 ft) wide beryllium mirror to reveal images 200 times beyond what has ever been sighted. (Picture credit: NASA; used with permission)

Sources and production

Beryllium is the 44th most abundant element and occurs naturally in the earth's crust, fossil fuels, air, and water. It is also found in trace quantities in foods although it has no known biological function in the human body. Beryllium was discovered in 1724 by Vauquelin, and later isolated independently by Bussy and Wöhler in 1828. Originally, it was named glucinium (Gl) after its sweet tasting oxide but in 1957, IUPAC adopted its present name. Commercial outlets for beryllium began in the 1920s, but its usage has increased over the years and its annual demand is estimated to approach 500 tonnes by 2018.[1] Mining of beryllium is only viable from a few of its minerals including beryl ($Be_3Al_2Si_6O_{18}$, 5 % by weight beryllium) and bertrandite [$Be_4(OH)_2Si_2O_7$, 15% by weight beryllium] in the United States, China, Kazakhstan, Mozambique, Brazil, Australia and Madagascar. Beryl also occurs naturally in New Zealand in pegmatite on the West Coast and Hawks Crag Breccia in the Buller Gorge.[2] However, over two-thirds of the world's beryllium is produced by the US while the rest comes from China, Kazakhstan and Russia. To extract beryllium, its minerals are first crushed and leached with acid to produce a beryllium salt solution from which the metal hydroxide is precipitated. Since the beryl crystals are more resistant to acid attack, it must first be melted at a high temperature. The stability of these minerals and their low beryllium content require expensive extraction techniques, making beryllium an expensive metal. The resultant hydroxide is further processed into beryllium's three most useful forms namely the pure metal, beryllium oxide, and its alloys with metals such as copper, nickel and aluminium.

Properties and uses

Beryllium is vital and indispensable in many of its applications. An understanding of the relevance of beryllium is best illustrated in its regard as a critical and strategic metal in the US and Europe. This is to highlight the impact its shortage or substitution could have on the economy, national security and defence. Interestingly, while the usage of beryllium in certain applications has been discontinued for safety reasons, new and crucial applications have emerged leading to its continuous demand and production.

The application of beryllium in aerospace and military equipment has been the most extensive. It is found in missiles, sensors, jet fighters, helicopters, landing gear, heat shielding and brakes for military and commercial aircrafts. Components made from beryllium are essential in spacecraft or military equipment because of its high strength which can sustain various structures without adding weight or losing strength from vibrations, thereby ensuring safety, precision and reliability in the end product. The high infra-red reflectivity of beryllium also makes it an ideal optical material for military, navigation and communication satellites, for instance, in the James Webb Telescope and Galileo Navigation Satellite System.

Besides aerospace and military applications, beryllium components have gained prominence in telecommunications, consumer and automobile electronics which now account for 45% of beryllium usage. The exceptional thermal conductivity and electrical insulation of beryllium ceramics makes it an excellent heat sink for electronic devices to support miniaturisation and the design of compact components. Furthermore, alloys containing beryllium in various proportions exhibits highly enhanced properties utilised for air bag sensors, electrical relays in automobiles, non-spark tools for oil and gas exploration, fatigue resistant springs and housing for undersea cables. In comparison with other metals, beryllium is very transparent to X-rays due to its low atomic number and is applied in X-ray windows for medical and scientific equipment.

Beryllium also possesses interesting nuclear properties. It is has a high neutron scattering cross section and is applied as a neutron moderator, reflector, and blast shields. In construction of nuclear fusion reactors, beryllium is a superior material for the lining of interior walls as it erodes more slowly and retains less of the plasma while the inclusion of beryllium oxide in fuels for nuclear fission can speed up cooling, thereby offering significant improvements to safety and efficiency of nuclear power plants.

Toxicity

Although beryllium possesses highly attractive properties and a variety of applications, it is also necessary to consider its toxicity and the hazards involved with the continual production and usage of the metal, its oxide and alloys. Beryllium is extremely toxic, both as a carcinogen and as an initiator of acute and chronic beryllium disease (CBD).[3-5] Although beryllium is considered a carcinogen, its carcinogenicity has only been established in animals while carcinogenicity in humans is still a subject of debate with recent studies questioning beryllium cytotoxicity.[3] Nevertheless, exposure to beryllium fumes or dust particles by inhalation and possibly dermal contact in certain individuals (1-15%) can lead to beryllium sensitisation and further progress into CBD. Chronic beryllium disease (CBD) is a debilitating granulomatous lung disorder resulting from an uncontrolled cell-mediated immune response marked by the proliferation of the $CD4^+$ T cells.[4] The dissolution, speciation and exact mechanism by which beryllium particles trigger CBD is not clearly understood. Current molecular understanding of the disease proposes that inhaled beryllium is detected by antigen-presenting cells which trigger the body's immune system into producing blood cells that engulf the particles forming granulomas that eventually harden the lungs causing respiratory abnormalities.[4] The onset of CBD can be delayed for over 20 years after exposure and there is no strong correlation between levels of exposure and CBD development, suggesting that a change in the beryllium speciation could be culpable. Interestingly, there is a genetic correlation to the disease as research evidences suggest that the risk of CBD is increased by the presence a specific gene- the HLA-DPB1.[5] Based on this, a beryllium lymphocyte proliferation test (BLPT) has been developed for routine use in diagnosis and workplace screening to predict susceptibility towards the disease. Another interesting correlation with CBD is that it is associated only with the processed forms of beryllium, such as beryllium metal and the oxide. Beryl and other ores of beryllium do not trigger a similar immune response possibly due to the lack of bioavailability of beryllium from these ore as they are insoluble in aqueous solution. It has also been observed that there is no beryllium oxo cluster (Be-O-Be) in the beryl structure ($Be_3Al_2Si_6O_{18}$), but rather silicon oxide units bridge beryllium and aluminium atoms.[4]

Beryllium in New Zealand

Beryllium is neither mined nor processed in New Zealand and although beryllium components are found in electronic devices and other consumer products, they are well encased and offer no hazard to general users.

However, appropriate disposal via the segregation of these components is recommended considering the imminent increase of beryllium in electronic waste. Exposure to beryllium can also result from the combustion of fossil fuels, especially coal which can contain significant amounts of beryllium. The main concern for beryllium exposure involves occupational related activities with beryllium components. The occupational exposure limit for beryllium in New Zealand is 2 μg m^{-3} for an 8 hour time-weighted average but it remains unclear if this limit actually excludes the development of CBD. No CBD case has been documented in New Zealand but a single beryllium sensitisation case was reported among aircraft maintenance staff in Air New Zealand.[6,7] The company thereafter set up a copper beryllium project in 2006, sampling work areas to identify and manage potential health risks to its workers involved in beryllium work areas. Noteworthy in their findings was the uncharted occupational hazards associated with beryllium-related operations in New Zealand.

The chemistry of beryllium

Beryllium is an s-block element with a relative atomic mass of u = 9.01218307(8) and an atomic number of z = 4. Its only naturally occurring isotope is ^{9}Be making it the only element having an even atomic number with one stable isotope. Beryllium has a density of 1.84 g cm^{-3} and is one of the lightest metals, second only to lithium, yet it has one of the highest melting points (1287 °C) amongst the light metals.

In comparison with its periodic table neighbours the coordination chemistry of beryllium has been relatively understudied due to its toxicity and a strong tendency towards hydrolysis. Solution techniques such as potentiometry and NMR are often utilised in the investigation of the coordination chemistry of the Be^{2+} cation and its interaction with ligands. ^{9}Be NMR has a narrow range of chemical shifts and suffers line broadening as a result of the quadrupolar beryllium nucleus ($S = 3/2$) and aqueous beryllium sulfate is used as the reference peak. Computational techniques are also invaluable and by the correlation of experimental and theoretical NMR chemical shifts, coordination to the Be^{2+} cation can be identified without isolating the resulting complex. This safe method for beryllium investigation has been pioneered by an author in our group.[8] Further research in our group utilises electrospray ionisation mass spectrometry (ESI-MS) as a solution technique for the cross validation of beryllium speciation. ESI-MS could be the technique of choice for the investigation of beryllium speciation in solutions, being able to transfer pre-existing solution species into the gas phase where they are analysed by the mass spectrometer. Importantly, this technique is sensitive, requiring only miniscule amounts of sample in solution thereby minimising any exposure to beryllium dust and allowing rich information on beryllium speciation to be gained from a study utilising only tiny quantities of beryllium compounds.

The coordination chemistry of beryllium is largely governed by its small size and high charge density. Its ground state electron configuration is 1s^2 2s^2 and the loss of the 2s^2 electrons leads to its only stable ion Be^{2+}. The small beryllium cation (31 pm) has a charge to size ratio (Z/r) of 6.45, which is comparable to the Al^{3+} cation (6.0) hence these two elements illustrate the typical periodic table diagonal relationship observed among the main group elements. Indeed, the chemistry of beryllium shows more similarities to aluminium rather than its heavier alkali earth metal congeners such as magnesium and calcium. For instance both elements exhibit a tendency to form strong covalent bonds, and form strongly solvated cations that are acidic and prone to hydrolysis. They also dissolve in non-oxidising acids or alkalis with the liberation of hydrogen. This striking similarity between the two metals resulted in beryllium being overlooked as a constituent of beryl until 1724. In fact even after beryllium's discovery, scientists presumed beryllium to have an oxidation state of +3 and placed it above aluminium in group 13 of the periodic table. However, aluminium still exhibits some differences from beryllium. Aluminium is a larger sized cation, therefore it prefers an octahedral geometry and is effectively complexed by EDTA while beryllium maintains a four-coordinate tetrahedral geometry and shows poor binding with EDTA.

Interaction with simple inorganic ligands

Generally, only a few inorganic ligands can compete with the hydroxyl ligand for a binding site with beryllium because in aqueous solution the Be^{2+} ion is strongly solvated. It also exhibits complex pH- and concentration-dependent aqueous speciation. In very acidic solution (pH < 3.5), without any ligand present, beryllium exists as the tetra-hydrated ion $[Be(H_2O)_4]^{2+}$. The high charge density of the Be^{2+} cation polarises the water molecules causing the negative end of their dipole to align toward itself while the protons are strongly repelled such that they are easily transferred, leaving the hydroxyl ion OH$^-$ in contact with the beryllium ion. Subsequent increases in pH or concentration yield several polynuclear hydroxo cluster species in varying degrees of abundance (Fig. 3). The trimer is the predominant hydroxo species and it exists as a cyclic six-membered ring structure with the four-coordination of the beryllium ion preserved by water molecules. NMR and potentiometric measurements[9,10] have characterised the $[Be(H_2O)_4]^{2+}$, $[Be_2(OH)]^{3+}$, and $[Be_3(OH)_3]^{3+}$ species while crystal structures of the picrate salt $[Be_3(\mu\text{-}OH)_3(H_2O)_6](picrate)_3{\cdot}6H_2O$ have confirmed the stability

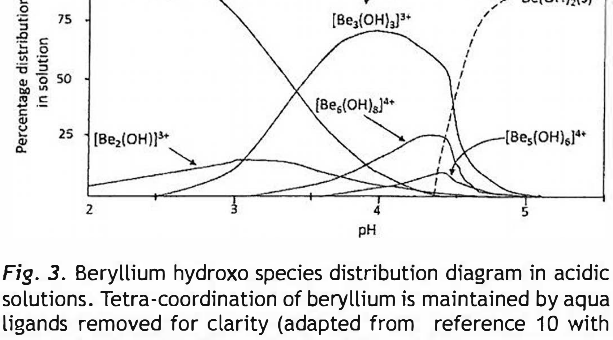


Fig. 3. Beryllium hydroxo species distribution diagram in acidic solutions. Tetra-coordination of beryllium is maintained by aqua ligands removed for clarity (adapted from reference 10 with permission from the Royal Society of Chemistry)

and cyclic nature of the trimeric species (Fig. 3).[11] The equilibrium is further complicated by other minor species in solution of which the $[Be_5(OH)_6]^{4+}$ and $[Be_6(OH)_8]^{4+}$ species offer the best fit for speciation data.[10] Between pH 5.5-12.0, insoluble beryllium hydroxide $Be(OH)_2$ precipitates. In solutions of higher alkalinity (pH > 12), this amphoteric $Be(OH)_2$ precipitate begins to dissolve, giving rise firstly to $[Be(OH)_3]^-$ and then, at even higher alkalinity, the tetrahydroxoberyllate dianion $[Be(OH)_4]^{2-}$ is formed. This occurs in the ^{9}Be NMR spectrum as a narrow peak at 2 ppm.[12] IR spectroscopy also proved the existence of this species with a characteristic IR band in the range of 700-750 cm^{-1}.[13] Several $M[Be(OH)_4]$ salts have been isolated[12] where M = Ca, Sr or Ba but a later attempt to resynthesise the $Ca[Be(OH)_4]$ complex (at pH 13.5-14) resulted in the isolation of a crystal whose structural investigation showed that it contained the hydroxoberyllate trianion, $[Be_2(OH)_7]^{3-}$, instead of the expected $[Be(OH)_4]^{2-}$ as previously assumed.[14] The $[Be_2(OH)_7]^{3-}$ anion was found to be associated with two calcium cations and a Z-shaped hydroxide hydrate anion $[HO\text{-}H\text{-}OH]^-$ which resulted in the $Ca_2[Be_2(OH)_7](HOHOH)(H_2O)_2$ complex.[14] The presence of yet another hydroxoberyllate anion $[Be_4(OH)_{10}]^{2-}$ was further identified by Schmidbaur *et al.* as crystals obtained from aqueous sodium beryllate solutions at high pH (13.2) result in the hydrated species $Na_2[Be_4(OH)_{10}](H_2O)_5$.[15] The tetraberylliumdecahydroxide dianion species was found to have a highly symmetrical adamantane structure where four beryllium atoms occupy the vertices of a regular tetrahedron with a terminal hydroxyl group at each metal centre while the remaining six bridging hydroxyl groups completed the tetra coordination to beryllium atoms.[15] The energetics for the existence of the $[Be_4(OH)_{10}]^{2-}$ anion can be explained by the condensation of the species $[Be(OH)_4]^{2-}$ with the extrusion of OH^- anions (Eq 1).

$$4[Be(OH)_4]^{2-} \underset{+2OH^-}{\overset{-2OH^-}{\rightleftharpoons}} 2[Be_2(OH)_7]^{3-} \underset{+4OH^-}{\overset{-4OH^-}{\rightleftharpoons}} [Be_4(OH)_{10}]^{2-} \qquad \text{(Eq. 1)}$$

The fluoride ion similarly exhibits high affinity for beryllium and was found to be the only inorganic ligand to form all four substitution products with water, $[Be(H_2O)_{4-n}F_n]^{(2-n)+}$ where n = 1-4. Based on equilibrium measurements,[16] it was found that the fluoride ion effectively competes with the hydroxo ligand up to pH 8, at which point $Be(OH)_2$ precipitates and species such as $[BeF_2(H_2O)_2]$ and $[BeF_3(H_2O)]^-$ exist in solution at a pH ranging from 0.5-8 in varying concentrations. The ^{19}F NMR spectra of these beryllium species give rise to signals of 1:1:1:1 quartet splitting due to coupling to the ^{9}Be nuclei.[12] In the ^{9}Be NMR spectrum, a mixture of species containing $[BeF(H_2O)_3]^+$, $[BeF_2(H_2O)_2]$ and $[BeF_3(H_2O)]^-$ can be distinguished as separate signals from an overall multiplet of a 1:1 doublet, a 1:2:1 triplet and a 1:3:3:1 quartet. The observation of the quartet in ^{19}F NMR suggests that the fluoride anions are attached to a single beryllium and that they do not form bridges between two beryllium atoms while the relative intensity of the signals shows that some of the hydrated BeF_2 species undergo ligand dissociation and redistribution in solution (Eq 2, 3).[12]

$$BeF_2 + 2H_2O \longrightarrow [BeF_2(H_2O)_2] \qquad \text{(Eq. 2)}$$

$$2BeF_2(H_2O)_2 \rightleftharpoons [BeF(H_2O)_3]^+ + [BeF_3(H_2O)]^- \qquad \text{(Eq. 3)}$$

Beryllium halides of the structure BeX_2 (X = F, Cl, Br, I) are not easily formed in the presence of water and often lead to different hydrolysis products. In most cases, in order to overcome this, harsh conditions of high temperatures and liquid ammonia are employed to form the halides by way of thermal decomposition. The dihydrogen phosphate ion $H_2PO_4^-$ is also known to replace water and results in the complexes $[Be_2(OH)(H_2PO_4)]^{2+}$ and $Be_3(OH)_3(H_2PO_4)_3$. NMR results further suggest the existence of another complex with the formula $[Be_3O(H_2PO_4)_6]^{2-}$ containing a 'beryllium acetate' type structure (see next section) where three beryllium ions are bound to a central oxygen atom with three phosphate units bridging the metals and the tetrahedral arrangement of the beryllium is completed by terminal phosphate ligands.[17]

Interaction with organic ligands

Recent research efforts have focused on beryllium speciation by ligands of interest with the objective of identifying suitable sequestering agents[18-21] as well as to obtain a clearer picture of the "mystic beryllium species" guilty of triggering an uncontrolled immune response in beryllium sensitisation and CBD.[4,22-25] Beryllium is highly oxophilic and a hard Lewis acid; therefore, it binds preferentially to hard donor atoms such as oxygen in carboxylates, hydroxyl and phosphate groups as well as nitrogen donors but to a lesser extent. Three themes have been central in studies of the interaction of beryllium with organic ligands, namely functional groups, chelate ring size and ligand geometry.

The significance of the chelate effect in beryllium's interaction with ligands is highlighted by the fact that bidentate dicarboxylate ligands have increased binding to beryllium compared to the monocarboxylate ligands, while dicarboxylate ligands possessing rigid structures that prevent chelation show poor binding with the beryllium ion.[12] Acetate, a typical monocarboxylate ligand, forms a polynuclear beryllium complex species $Be_4O(O_2CCH_3)_6$ where six acetates act as bridging ligands for four beryllium atoms.[16] In contrast to this, the dicarboxylate ligands reveal beryllium species of the types $[Be(H_2O)_2L]$, $[BeL_2]^{2-}$ and $[Be_3(OH)_3(L)_3]^{3-}$.[16] The trimeric hydroxo/dicarboxylate species $[Be_3(OH)_3(L)_3]^{3-}$ was further crystallised, highlighting the stability of the hydroxo trimer and the competing hydrolytic tendency in the presence of other ligands in aqueous solution.[17] Further support for enhanced interaction and stability of beryllium with ligands that form suitable chelate rings can be shown by a survey of formation constants (log *k* values) among analogous ligands of varying chelated ring size (Fig. 4). Ligands that form six-membered rings with beryllium are the most stable for the binding of beryllium since they offer the most compatibility for a tetrahedral geometry with the small sized Be^{2+} cation. Consequently, malonate which forms a six-membered ring binds beryllium more strongly than oxalate which forms a five-membered ring, while succinic and maleic acids which form seven-membered chelate rings also reveal weaker binding. Chromotropic acid, the strongest bidentate ligand for beryllium, forms a six-membered chelate ring.

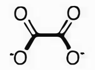
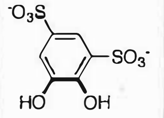
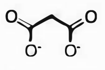
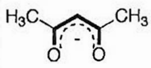
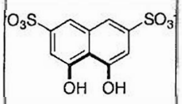
Chelate ring size	**Dicarboxylate**	**Diketonate**	**Dihydroxy**
Five	 Oxalate (4.08)	 Tropolonate (8.40)	 Tiron (13.50)
Six	 Malonate (5.91)	 Acetylacetonate (12.36)	 Chromotropic acid (16.34)

Fig. 4. Formation constant (log *k*) of beryllium complex among analogous ligands of 5 and 6 membered chelate rings (Log *k* values from reference 13)

The interactions of the beryllium ion with hydroxycarboxylate ligands have been extensively investigated because they exhibit significant binding with beryllium and can serve as models for ligands of biological interest. In fact, the aromatic hydroxycarboxylate aurin tricarboxylate (aluminon) was earlier developed for chelation therapy in beryllium poisoning.[13] In a remarkable contrast, aliphatic hydroxycarboxylates generally show a weaker interaction with beryllium with the exception of citric acid. Citric acid is an excellent ligand for beryllium capable of solubilising beryllium at molar concentrations across the entire pH range.[23] It binds beryllium in a polynuclear fashion with a metal to ligand ratio of 2:1 (Fig. 5a). To further understand the strong binding of citric acid with beryllium, six other aliphatic hydroxylcarboxylic acids have been studied, each chosen to highlight the relevance of the hydroxyl or carboxylate functionality toward a strong beryllium chelation. Competition experiments have shown that the significant binding of beryllium to citric acid could be attributed to the formation of a five- and six-membered ring Be-O-Be motif via a bridging hydroxyl group.[23] In agreement with this, two aromatic analogues, 2-hydroxyisophthalic acid (Fig. 5b) and 2,3-dihydroxybenzoic acid (Fig. 5c), which offer a similar polynuclear binding pocket for beryllium via a carboxylate and a bridging hydroxyl group, revealed an even stronger interaction with beryllium as well as excellent selectivity in the presence of other metal ions.[22] This development is of particular interest considering the abundance of similar functionalities in the major histocompatibility complex (MHC) class II receptor gene implicated for the genetic susceptibility in CBD cases.

However, other ligands lacking the characteristic polynuclear binding pocket of citric acid have equally been observed to bind beryllium strongly (Fig. 6). An example is 10-hydroxybenzo[*h*]quinoline-7-sulfonate (HBQS) (Fig. 6a) which binds beryllium extremely well and is now part of a commercial beryllium detection system.[26] This has led to the proposition that the beryllium cation actually interacts strongly and is bonded by ligands possessing a hydrogen bonded proton that can easily be displaced by the similarly small but tetrahedral Be^{2+} cation.[25] These ligands also possess high pKa values and Fig. 6 shows some examples. This concept was further explored in identifying the tri-dentate ligand 2,6-bis(2-hydroxyphenyl)pyridine (BHPP) (Fig. 6b) as a fluorescent Be indicator for cellular studies as it is able to detect and solubilise beryllium in phosphate media under physiological conditions.[27] X-ray crystal structure of the Be(BHPP) complex revealed that the metal is coordinated in a tetrahedral geometry by the pyridine nitrogen and the two oxygen donors of the phenolic groups while the fourth coordination site is taken up by a water molecule. This understanding of beryllium's interaction with ligands possessing suitable sites of strong hydrogen bonding offers new insight into the binding of beryllium to proteins and other biomolecules relevant for the biomolecular understanding of how beryllium triggers CBD.[24]

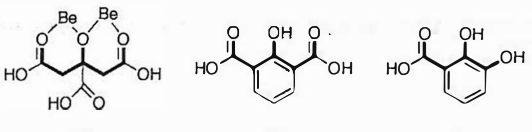

(a) (b) (c)

Fig. 5. 2:1 Be-citric acid complex (a) and similar ligands (2-hydroxyisophthalic acid (b) and 2, 3-dihydroxybenzoic acid (c)), possessing polynuclear binding pocket for beryllium via a carboxylate and a bridging hydroxyl group

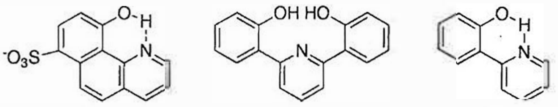

(a) (b) (c)

Fig. 6. Ligands possessing strongly bonded hydrogen sites suitable for beryllium binding: (a) 10-hydrobenzo(h)quinolone-7-sulfonate (HBQS), (b) 2,6-bis(2-hydroxyphenyl)pyridine (BHPP), (c) 2-(2-hydroxyphenyl) pyridine

An alternative geometry for beryllium binding which forms the central theme of research in our group involves tetra-dentate ligands which potentially encapsulate the Be^{2+} cation (Fig. 7). This is illustrated in the binding of nitrilotripropionic acid to beryllium (Fig. 7a). Nitrilotripropionic acid binds beryllium through the central amine and the three carboxylate groups which wrap round the Be^{2+} cation creating six-membered chelate rings with appropriate tetrahedral geometry.[28] Ligands such as phthalocyanine (Fig. 7b), although tetradentate, do not provide a tetrahedral arrangement of donor atoms however, a chiral binapthyldiimine- Be(II) complex (Fig. 7c) analysed in solution by Plieger *et al.* have revealed a tetrahedral coordination with the Be^{2+} cation suggesting that selective uptake of Be^{2+} could possibly be attained by incorporating mixed N/O donor atoms as in polyaminocarboxylic acids.[13,19] Potentiometry and NMR spectroscopy[28] have further supported the selectivity of a mixed N/O donor ligand and the ligands nitrilotripropionic acid and nitriloaceticdipropionic acid revealed selective uptake of Be^{2+} in the presence of Mg^{2+}. However, the flexibility afforded by the alkyl arms used for encapsulation cannot effectively preclude the ligand binding to larger metal cations.[21] Therefore, nitrilotripropionic acid-type ligands have further been investigated in a study which incorporated the rigidity of aromatic groups to enhance selectivity (Fig. 8).[20,21] Full encapsulation of the beryllium cation by these ligands was validated by correlating experimental and theoretical Be NMR chemical shifts, while the synthetic variation of the chelate ring size and the donor atom in one of the encapsulation arms (Fig. 8) reiterated beryllium's binding preferences. Significantly, this study revealed that the combination of unfavourable features in ligands such as weakly coordinating donors and five-membered chelate rings results in weaker binding with the Be^{2+} cation. For instance, the calculated ^{9}Be NMR chemical shifts for the beryllium complexes with ligands shown in Fig. 8a and 8b did not correlate well with the experimental shifts, suggesting that they might not be able to fully encapsulate the Be^{2+} cation like the ligands in Figs. 8c-f, which offer either a strongly coordinating oxygen donor or an unstrained six-membered chelate ring .[20,21]

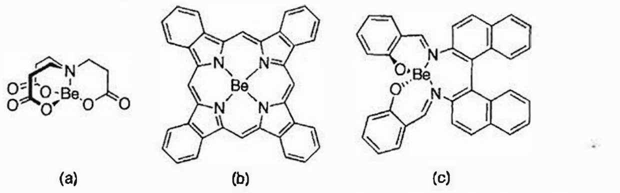


Fig. 7. Tetradentate coordination of beryllium to (a) phthalocyanine (b) nitrilotripropionic acid (c) chiral binaphthyldiimine ligand

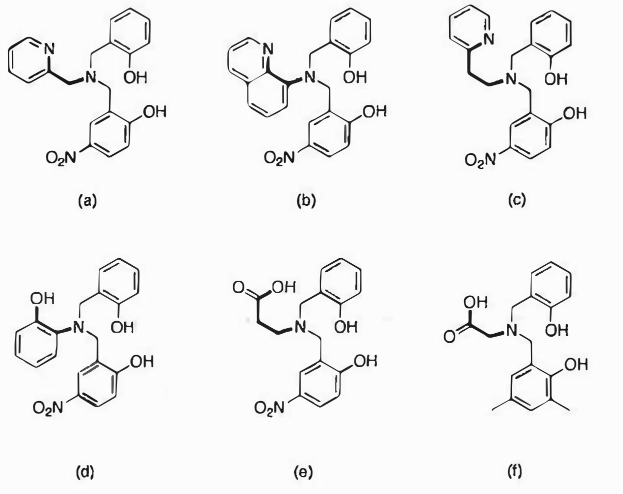


Fig. 8. Nitrilotripropionic acid-type ligands for the full encapsulation of beryllium

Another functional group relevant for beryllium binding is the phosphonate group but fewer studies have investigated the solution chemistry of beryllium phosphonate complexes despite the fact that phosphonate ligands (PO moiety) form stronger complexes than carboxylate/hydroxyl ligands (CO moiety). For instance, methylphosphonate, a monodentate ligand, forms a stronger complex than the malonate ligand while methylenediphosphonate, which offers a similar six-member chelate ring as malonate, reveals a much stronger interaction with beryllium.[29] Using potentiometric and multinuclear NMR methods, the interaction of beryllium with some phosphonate ligands have been ordered as malonate<methylphosphonate<phosphonopropionate<phosphonoacetate<methylenediphosphonate. The structures and chelate ring sizes of these ligands are shown in Fig. 9. The superior interaction of the PO moiety with beryllium is again revealed in the stronger interaction of methylenediphosphonate over phosphonoacetate. Both ligands differ only in a second donor site. Methylenediphosphonate possesses two phosphonate groups while the phosphonoacetate coordinates via a phosphonate and carboxylate group. The stronger binding of methylenediphosphonate and phosphonoacetate over phosphonopropionate is presumably due to the latter forming a seven membered chelate ring.[30] Accordingly, all the bidentate ligands in Fig. 9 containing phosphonate groups exhibit superior binding with beryllium compared to the monodentate methylphosphonate. This is relevant since metal complexes of nucleotides containing the phosphate groups such as adenosine 5-monophosphate, -diphosphate (ADP) and –triphosphate (ATP) play a fundamental role in biological processes. Potentiometric titrations[31] have revealed higher stability constants for the $[Be(ATP)]^{2-}$ species (log k = 6.52) compared with the corresponding $[Mg(ATP)]^{2-}$ species (log k = 4.10) and beryllium is also known to inhibit alkaline phosphatase and DNA replication.[32] Using a competitive fluorimetric approach, it was further observed that the decrease in the number of phosphate groups from ATP to ADP resulted in a remarkable decrease in binding affinity confirming that the Be^{2+} cation is chelated by adjacent phosphate groups in ATP.[33] Ferritin is also another phosphate binding biomolecule. It is an iron storage protein that reveals significant binding with beryllium and is likely to provide binding sites that allow beryllium to pass through cellular systems.[4,33]

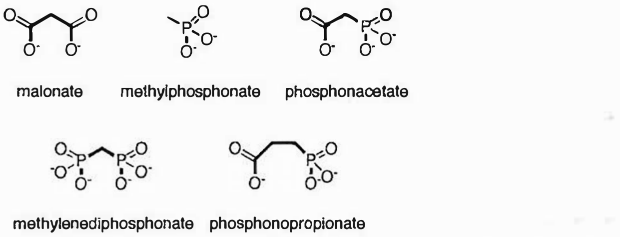


Fig. 9. Malonate and ligands with the phosphonate functionality

Conclusions

Beryllium is a very useful speciality metal and is indispensable in several of its applications. However, its usage should be limited considering its toxicity and strict industrial and government controls should be administered to reduce future potential exposure of beryllium in New Zealand workplaces. Substitutes for beryllium metal and alloys include titanium and pyrolytic graphite, while beryllium oxide can be replaced by aluminium nitride. Unfortunately, these substitutes often result in a notable reduction in the performance of the end product and this has led to a sustained usage of beryllium. It is important, therefore, to identify selective and tight binding ligands with suitable functional groups and arrangement of donor atoms for applications in the area of beryllium detection, remediation and chelation therapy. Research in our group is building a greater understanding of the coordination chemistry of the Be^{2+} cation for the development of sequestering agents that will potentially encapsulate beryllium for selective uptake. Meanwhile, other studies on the bioinorganic chemistry of beryllium hold the key to unravelling the mystery of the uncontrolled immune system's response to beryllium particles.

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