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Beryllium coordination chemistry

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CONTENTS

ABSTRACT

The coordination chemistry of beryllium with particular emphasis on chelates under physiological or near physiological conditions is surveyed. Hard donors such as oxygen are emphasized; equilibrium data and formation constants are reported as an indication of the strength of the complex.

A. INTRODUCTION

Beryllium is the most toxic non-radioactive element in the Periodic Table [1]. It is also the second lightest metal after lithium and its unique properties are a great asset in today's nuclear, aerospace and electronic industries. A wide variety of applications have been developed, ranging from aircraft landing gear bushings to undersea telephone cable housings; and from oil field drilling equipment to golf clubs [2,3]. The demand for beryl-

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lium is currently increasing at a rate of ca. 3–5% annually. The 1985 world production was ca. 400 tonnes of beryllium [4]. A further expansion in its utilization is hindered by its high price, its complex processing and its toxicity. In September 1990, an accident occurred in a nuclear fuel processing plant in Ust-Kamenogorsk of the Soviet Union resulting in tonnes of beryllium being released into the atmosphere [5]. The lack of awareness of the dangers of beryllium poisoning was again highlighted.

Beryl, ($Al_2Be_3Si_6O_{18}$), and bertrandite, ($Be_4(OH)_2Si_2O_7$), remain the principal minerals for the extraction of beryllium, and it is here that occupational hazards are most apparent. Although oral ingestion of beryllium compounds is of minimal concern, inhalation of minute amounts (threshold limit value (TLV) = 0.002 mg m^{-3}, cf. HCN, TLV = 10 mg m^{-3}) [6] may lead to both acute and chronic effects. An interesting feature of beryllium poisoning is that it generally appears only after a significant latent period, most commonly 5–9 years after termination of exposure. The toxicological, biomedical and environmental aspects of beryllium are well documented [3,7,8], however little is known about the biochemistry of Be^{II}, and the biochemical mechanism of beryllium toxicity remain speculative. Therefore, there is much interest in the search for suitable ligands as antidotes for beryllium poisoning [9].

There is at present no universally accepted antidote for beryllium poisoning. Problems are encountered due to the toxic nature of the antidotes and the time elapsed before its administration. In the event of beryllium poisoning, increased oxygen inhalation, judicious use of steroids, and absolute bed rest are necessary (there is no clear evidence that steroids have cured chronic beryllium poisoning). Skin poisoning requires surgical removal and, in severe cases, amputation may be required [10].

In this review, we have surveyed the literature on the coordination chemistry of beryllium with particular emphasis on chelates under physiological or near physiological conditions. Where possible, equilibrium data have been quoted as formation constants are good indicators of the strength of the complex in solution. This will serve as the basis for further development in our understanding of the coordination chemistry and the factors involved in designing Be^{II} sequestering agents. "Hard" oxygen donor ligands which bind strongly to the "hard" Be^{2+} cations are highlighted as these donors reflect the likely prerequisites for successful complexation. Other aspects of beryllium chemistry are more briefly outlined with leading references for further reading. No attempt has been made to cover all aspects of beryllium coordination chemistry. References used in much of the earlier work describing the coordination chemistry are given by Everest [11]. The equilibrium data from the literature up to 1971 are given by Sillén and Martell [12].

As far as possible, organoberyllium and theoretical beryllium chemistry have been omitted. It is interesting to note that the number of theoretical papers on beryllium chemistry outweigh those by experiment. Coates and co-workers [13,14] have covered the majority of organoberyllium chemistry up to 1974. Recent reviews and publications on both organometallic and theoretical work [15–20] give leading references to the subject areas. Hubberstey's reviews [15] also cover recent research on other aspects of beryllium chemistry through his surveys on *The Elements of Group 2*.

B. SOLUTION CHEMISTRY

The important aspects of the solution chemistry of the hydrated Be^{2+} ion in both acid and alkaline media, reported until 1964, have been dealt with by Everest [11]. This includes values for the hydration of the Be^{2+} ion and the effects caused by the high charge to radius ratio. The most important feature of the hydrated Be^{2+} ion is its ready hydrolysis to give polynuclear species such as $[Be_n(OH)_n]^{n+}$, where $n = 2$–4.

In 1956, Kakihana and Sillén [21] carried out the first extensive study of Be^{2+} in aqueous solution. They concluded that $[Be_3(OH)_3]^{3+}$ (**1**) was the predominant species; $[Be_2(OH)]^{3+}$ (**2**) and $Be(OH)_2$ (**3**) formed as the minor components under the experimental conditions considered. The complex **1** was described as a cyclic structure in which the beryllium ions are linked by hydroxyl bridges and the four coordination of the beryllium ion is preserved by six water molecules (Fig. l) Since 1956, there have been many efforts to gain more chemical information on the hydrolytic behaviour of beryllium in aqueous solution. For the reaction,

$$pBe^{2+} + qH_2O \rightleftharpoons [Be_p(OH)_q]^{(2p-q)+} + qH^+ \quad (1)$$

the equilibrium constant may be defined as

$$\beta_{pq} = \frac{[Be_p(OH)_q^{(2p-q)+}][H^+]^q}{[Be^{2+}]^p} \quad (2)$$

Recent equilibrium data have been reported by Bruno [22], Maeda et al. [23] and Brown et al. [24] with equilibrium constants for complexes **1**, **2** and **3**, respectively from each author, of $-\log_{10}\beta_{33} = 8.656 \pm 0.002$, 8.700 ± 0.002 and 8.804 ± 0.002, $-\log_{10}\beta_{21} = 3.23 \pm 0.05$, 3.52 ± 0.07 and 2.955 ± 0.007, and $-\log_{10}\beta_{12} = 11.09 \pm 0.04$, 11.54 ± 0.06 and 11.320 ± 0.008. It is now believed that species present upon hydrolysis also include $[Be_5(OH)_6]^{4+}$ and $[Be_6(OH)_8]^{4+}$ in solution. These papers have also surveyed other hydrolytic investigations in this area up to the mid-1980s. It is important to note that in most of the formulations described above, sophisticated computational and theoretical analysis have been used to support the occurrence of the proposed polynuclear hydroxo

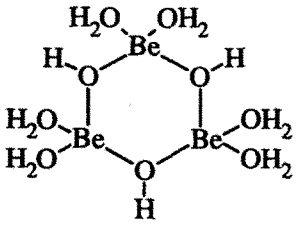


Fig. 1. Proposed structure of the hydrated $[Be_3(OH)_3]^{3+}$ (**1**).

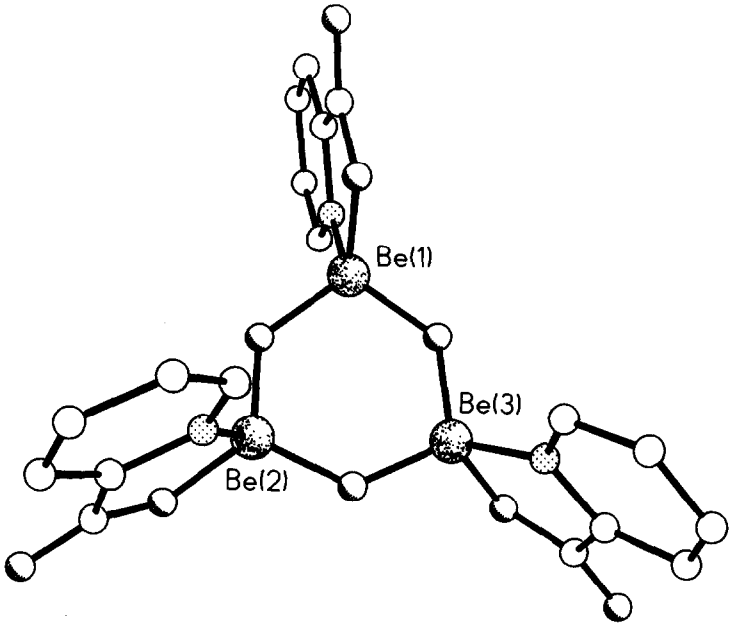


Fig. 2. X-Ray structure of $Be_3(OH)_3(pic)_3$, where pic = picolinate.

complexes. Kakihana and Sillén's description of **1** was confirmed in 1974 when the X-ray single-crystal structure of $Be_3(OH)_3(pic)_3$ (**4**), where pic = picolinate, was determined by Faure et al. [25] (Fig. 2). This, together with the solution studies, reflects the high stability of the "$Be_3(OH)_3$" moiety.

Connick and Fiat [26] used ^{17}O NMR spectroscopy to confirm the number of water molecules in the first coordination sphere of the Be^{2+} cation. By using ^{17}O enriched water, Connick and Fiat were able to separate ^{17}O NMR signals arising from the paramagnetically shifted free $H_2{}^{17}O$ molecules and the comparatively unshifted $[Be(H_2{}^{17}O)_4]^{2+}$ cations.

The first vibrational spectroscopic assignment of alkaline beryllate solutions was carried out by Kulikova et al. [27]. The aquo-complex, $[Be(H_2O)_4]^{2+}$ (**5**), has characteristic bands at 520 cm^{-1} and 870–900 cm^{-1}. The band at 520 cm^{-1} is both infrared and Raman active and has been unambiguously assigned, by deuteriation, as the $\nu_1(A_1)$ skeletal

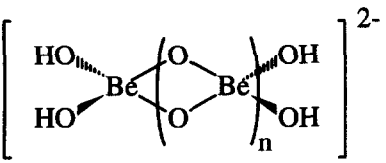


Fig. 3. $[Be_{n+1}(OH)_{2n+4}]^{2-}$ polymers.

vibration. The band at 870–900 cm^{-1} is infrared active. Data have been obtained, supporting the assignment of the infrared bands in the range 700–750 cm^{-1} to the $[Be(OH)_4]^{2-}$ (6) complex. Based on ^1H NMR intensity measurements, Akitt and Duncan [28] have shown the presence of **1**, **2** and **5** in the hydrolysis reaction of **5**. Further evidence by NMR was given for exclusive four-coordinate beryllium in solution.

To summarize, on dissolution in water, beryllium salts rapidly hydrolyze to give a series of hydroxo complexes, initially forming mainly the trimer **1**, and higher polymers near the point of precipitation. Further addition of alkali produces polymeric species of the form $[Be_{n+1}(OH)_{2n+4}]^{2-}$ (Fig. 3) until ultimately the mononuclear beryllate anion **6** is formed.

C. INORGANIC SALTS

The preparation and properties of inorganic beryllium salts have been discussed by Everest [11]. However, the salts are often used as starting materials for the formation of beryllium complexes and properties which may be of synthetic relevance are addressed here. Table 1 lists some of these salts giving solubility in water, equilibrium data, and references where applicable. Both solubility and formation constants are noteworthy factors in the study of beryllium chelation in solution. These properties are therefore highlighted.

Beryllium oxosalts including the carbonate, sulphate, selenate and nitrate, all exist as tetrahydrates, and the iodate was described as a dodecahydrate [37]. These often heavily hydrated salts of beryllium have been known for many years. As far back as 1923, Ficke and Schützdeller [38] concluded that the Be^{2+} ion is the most heavily hydrated of all the bivalent ions.

TABLE 1

Formation constants and water solubility of some beryllium salts

Ligand	Formation constants (log_{10})	Solubility in water		Ref.
		Cold	Hot	
F^-	β_4 13.1, 13.4	Infinite	Infinite	29, 30
Cl^-	K_1 1.11, β_2 0.30, β_3 1.40	Very soluble	Very soluble	31
Br^-	K_1 –0.7, β_2 –0.8	Soluble	Very soluble	32
SO_4^{2-}	β_2 1.78, β_3 2.08	42.5[a]	100[b]	33
NO_3^-	K_1 –0.60, β_2 1.62	Very soluble	Very soluble	34, 31
$P_3O_{10}^{5-}$	$K(BeHL^{2-})$ –5.35			35
$P_2O_7^{4-}$	$K(BeL^{2-})$ 10.08			36
	$K(BeHL^-)$ 5.98			
	$K(Be_2L)$ 5.37			

[a] g per 100 cm^3, 25°C.
[b] g per 100 cm^3, 100°C.

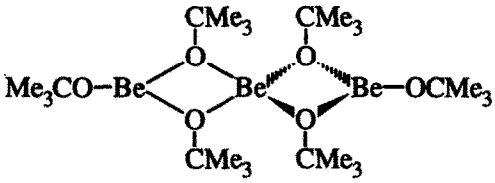


Fig. 4. Proposed structure of the trimer, $[Be(O^tBu)_2]_3$ (7).

D. BERYLLIUM ALKOXIDES

Relatively little work has been done on beryllium alkoxides compared to other alkoxides of Group 2. This is despite the fact that in 1929 Schmidt [39] reported the synthesis of beryllium ethoxide by the reaction of metallic beryllium in ethanol catalyzed by iodine or mercuric chloride. Coates and co-workers [40] have synthesized various beryllium and alkylberyllium alkoxides, by addition of alcohol to an ethereal solution of dimethyl beryllium. Depending on the conditions and the alcohol, the species may be di- or trimeric. On the basis of ^1H NMR and cryoscopy data, trimeric $[Be(O^tBu)_2]_3$ (7) (Fig. 4) and dimeric $[Be(OCEt_3)_2]_2$ (**8**) (Fig. 5) have been proposed. The X-ray crystal structure of the trimer $[Be(NMe_2)_2]_3$, which is "isoelectronic" with 7, was reported in 1967 [41]. The proposed structures of the oligomeric beryllium alkoxides containing bridging alcohols have been recently confirmed by X-ray studies of haloberyllium alkoxides with tert-butanol as the bridging ligand for the formation of di- and trimeric species such as $(BrBeO^tBu \cdot OEt_2)_2$ (Fig. 6) [42] and $[Cl_2Be_3(O^tBu)_4]$ (**9**) (Fig. 7) [43], respectively.

A number of aluminium and beryllium bimetallic alkoxides have been described by Aggrawal and Mehrotra [44]. On the basis of infrared and NMR spectroscopic data, they proposed the formation of $Be[Al(OR)(OR')_3]_2$ (Fig. 8) where R = R' = Me, Et, ^{n}Pr, ^{n}Bu, ^{i}Bu, ^{s}Bu, ^{i}Am; R = ^{i}Pr, R' = ^{t}Bu, ^{t}Am. There is a strong tendency for beryllium to achieve maximum (fourfold) coordination. In unidendate ligated BeL_2 complexes, maximum coordination can be achieved by the use of bridging ligands, thus forming $[BeL_2]_n$ polymers. Three-coordinate beryllium atoms (e.g. 7, **8** and **9**) and two-coordinate beryllium atoms (e.g. $Be(CMe_3)_2$ [45], $Be[N(SiMe_3)_2]_2$ [46] and bis-(2,6-di-tert-butyl-phenoxy)beryllium [47]) are unusual and exist only as a result of steric constraints. The steric bulk of the ligand may also lower the degree of polymerization (e.g. 7 is trimeric

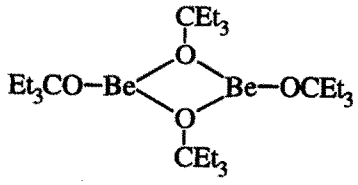


Fig. 5. Proposed structure of the dimer, $[Be(OCEt_3)_2]_2$ (**8**).

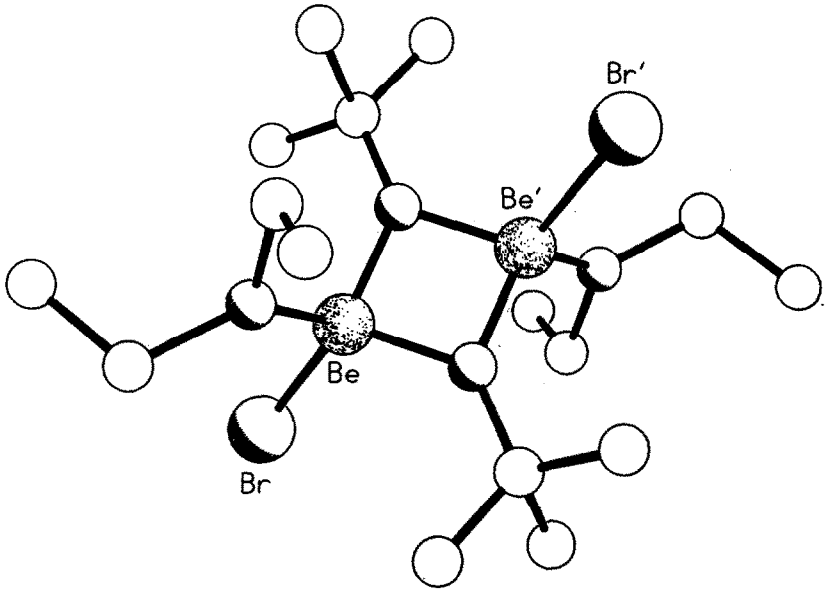


Fig. 6. X-Ray structure of $(BrBeO^tBu \cdot OEt_2)_2$.

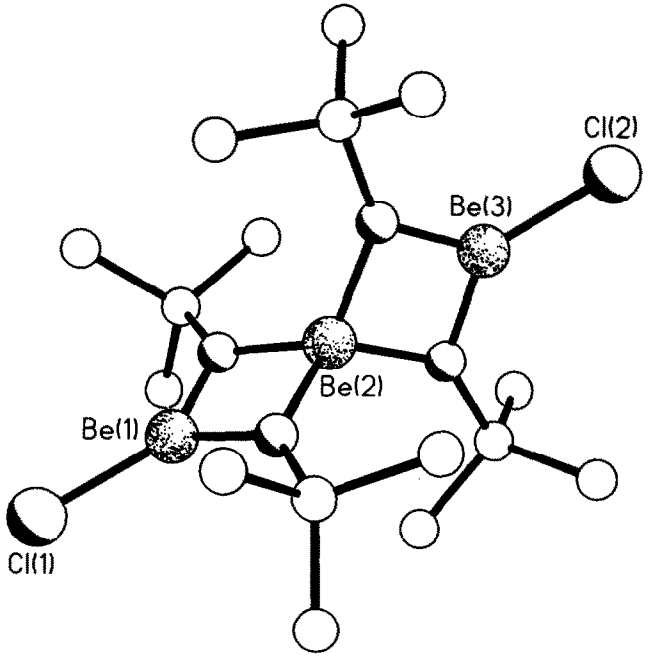


Fig. 7. X-Ray structure of $[Cl_2Be_3(O^tBu)_4]$ (9).

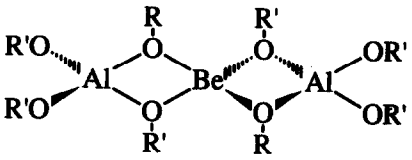


Fig. 8. Proposed structure of $Be[Al(OR)(OR')_3]_2$ type complexes, where R = R' = Me, Et, ^{n}Pr, ^{n}Bu, ^{i}Bu, ^{s}Bu, ^{i}Am; R = ^{i}Pr, R' = ^{t}Bu, ^{t}Am.

and **8** is dimeric). As one might expect, beryllium alkoxides are highly susceptible to hydrolysis. Therefore, the alkoxides play an insignificant role in the biological aspects of beryllium chemistry, however, they provide some informative data on the unique behaviour of the Be^{2+} cation.

E. BERYLLIUM OXIDE CARBOXYLATES

The carboxylate moiety, RCO_2^-, possesses two oxygen atoms both of which have the capacity to donate electrons. Bidenticity is not observed for beryllium due to the large "bite" generated between the two oxygen atoms. However, both oxygen atoms are utilized by donation to different beryllium atoms, thus forming polynuclear species. The oxide carboxylate, $Be_4O(O_2CR)_6$, was first demonstrated in 1901 with the synthesis of beryllium oxide acetate or "basic beryllium acetate", $Be_4O(O_2CMe)_6$ (**10**) (Fig. 9), by Urbain and Lacombe [48]. The cubic structure was later confirmed by several independent workers using X-ray analysis [49–52]. The structure may be described as four beryllium atoms tetrahedrally arranged with an O^{2-} in the centre and the four-coordination of beryllium preserved by six bridging acetates along the edges of the

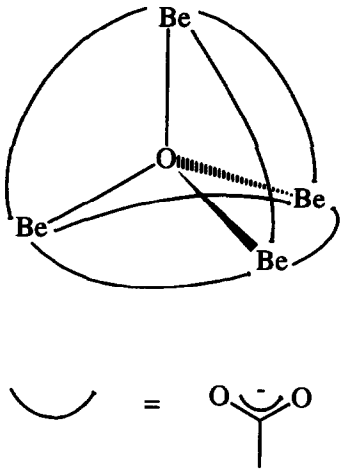


Fig. 9. Structure of "basic beryllium acetate", $Be_4O(O_2CMe)_6$ (**10**).

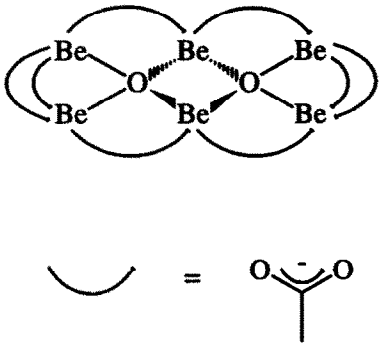


Fig. 10. Structure of $Be_6O_2(O_2CMe)_8$.

tetrahedron. The principal synthetic route is by reaction of the organic acid or acid anhydride with beryllium oxide or hydroxide [53]. Transitions observed in the solid phase at higher temperatures (e.g. cubic to monoclinic), methods of synthesis and reactivities with various reagents are summarized by Everest [11]. In 1975, Atovmyan et al. [54] reported the structure of $Be_6O_2(O_2CMe)_8$ which has a novel structure consisting of two μ_4 oxygen atoms and can be likened to an inverse B_2H_6 molecule with the four-coordination of beryllium preserved by eight bridging acetates (Fig. 10). $Be_4O(NO_3)_6$ was first synthesized by Addison and Walker [55]; Sipachev et al. [56,57] subsequently confirmed the μ_4-oxo structure analogous to that of **10** by fragmentation under electron impact and gas-phase electron diffraction studies.

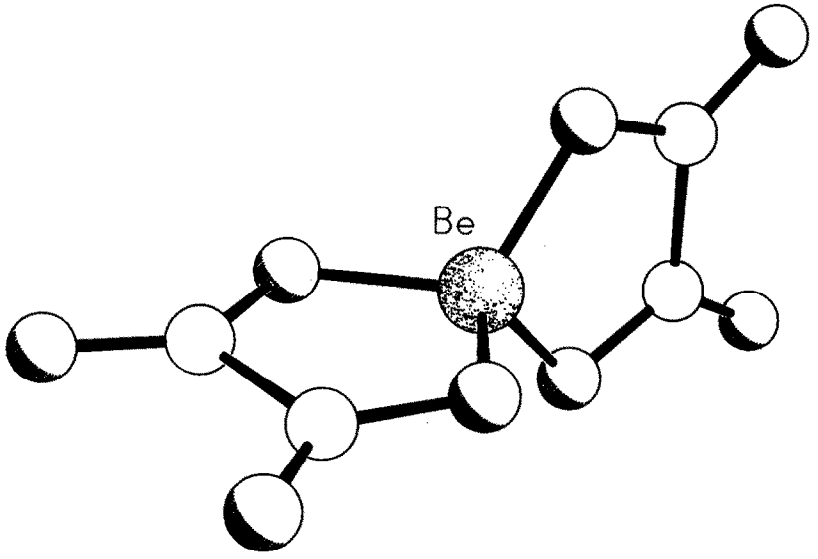
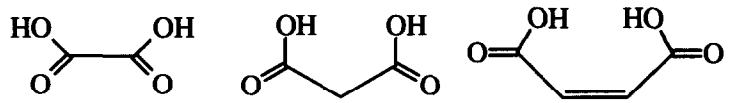


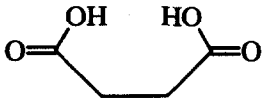
Fig. 11. X-Ray structure of bis-(oxalato)beryllium.



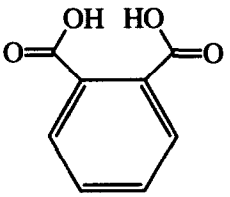
Oxalic acid (Ethanedioic acid) **11**

Malonic acid (Propanedioic acid) **12**

Maleic acid (*cis*-Butenedioic acid) **13**



Succinic acid (Butanedioic acid) **14**



Phthalic acid (Benzene-1,2-dicarboxylic acid) **15**

Scheme 1. Dicarboxylic acids.

F. DICARBOXYLIC ACIDS

It is well known that complexes formed with metal ions are most stable with five- or six-membered chelate rings (a more detailed study of chelate ring size on metal ion selectivity has recently been reported [58]). Therefore, it is not surprising that considerable volume of work has been reported on beryllium complexes derived from oxalic and malonic acids. In fact, the crystal structure of both bis-(oxalato)beryllium and bis-(malonato)beryllium dianions have been reported [59,60] (Figs. 11,12). Both structures show the preservation of tetrahedral beryllium by the chelating oxygens. However, a comparison of the O–Be–O angles (Table 2) suggests that the beryllium atom in the malonato complex is less distorted from a true tetrahedron and hence less strained in the solid state.

In 1962, De Bruin et al. [61] reported the titrametrically determined stability constants (eqns. (3) and (4)) for beryllium complexes derived from **11** to **15** (Table 3). The higher stabilities of the malonate complex is again a reflection of the better "fit" in solution as was observed in the solid state. Duc et al. [63] reported a more refined potentiometry experiment on **12** and **14** beryllium derivatives. Apart from the standard stepwise equilibrium constants for BeL (**16**) and $[BeL_2]^{2-}$ (**17**), $[Be_3(OH)_3L_3]^{3-}$ (**18**) was

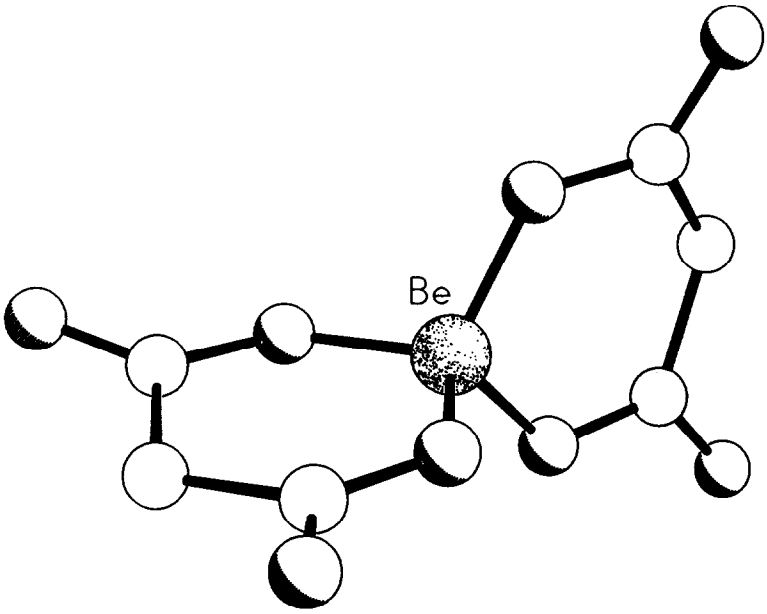


Fig. 12. X-Ray structure of bis-(malonato)beryllium.

also identified for both systems and species corresponding to $Be(HL)_2$ and $[Be_3(OH)_3HL]^{2+}$ were described for the succinate system.

$$Be^{2+} + L^{2-} \rightleftharpoons [BeL] \qquad K_1 \tag{3}$$

$$[BeL] + L^{2-} \rightleftharpoons [BeL_2]^{2-} \qquad K_2 \tag{4}$$

Jaber et al. [62] characterized species **16–18**, derived from oxalic acid, by infrared and Raman spectroscopy. By measuring the intensities of the Raman scattering spectra

TABLE 2

O–Be–O bond angles (°) of $K_2[Be(C_2O_4)_2]$ and $K_2[Be(CO_2CH_2CO_2)_2]$

$K_2[Be(C_2O_4)_2]$[a]		$K_2[Be(CO_2CH_2CO_2)_2]$[b]	
O(2)–Be–O(3)	99.6(2)	O(1)–Be–O(3)	109.3(2)
O(2)–Be–O(6)	115.4(2)	O(1)–Be–O(5)	111.0(2)
O(3)–Be–O(6)	113.8(2)	O(3)–Be–O(7)	107.1(2)
O(6)–Be–O(6')	99.7(2)	O(3)–Be–O(5)	109.6(2)
		O(1)–Be–O(7)	111.4(2)
		O(5)–Be–O(7)	108.3(2)

[a]Ref. 59.
[b]Ref. 60.

TABLE 3

Formation constants for some dicarboxylic derivatives of beryllium

Acid	$\log_{10} K_1$	$\log_{10} \beta_2$	$\log_{10} \beta_x$	$\log_{10} \beta_y$
Oxalic	4.08[a], 3.26[b]	5.91[a], 5.32[b]	39.94[b]	
Malonic	5.73[a], 5.35[c]	9.28[a], 8.85[c]	0.89[c]	
Succinic	4.69[a], 2.74[c]	6.43[a], 4.36[c]	5.07[c]	2.00[c]
Maleic	4.33[a]	6.46[a]		
Phthalic	3.97[a]	5.69[a]		

$\beta_x = [Be_3(OH)_3L_3^{3-}]/[Be^{2+}]^3[OH^-]^3[L^{2-}]^3$ for the oxalate complex.
$\beta_x = [Be_3(OH)_3L_3^{3-}]/[Be_3(OH)_3^{3+}][L^{2-}]_3$ for malonate and succinate complexes.
$\beta_y = [Be_3(OH)_3HL^{2+}]/[Be_3(OH)_3^{3+}][HL^-]$.
[a]Ref. 61.
[b]Ref. 62.
[c]Ref. 63.

over a pH range, stability constants were calculated (Table 3). Subsequently, Jaber and Thomas-David [64] studied the beryllium malonate complex using ^9Be and ^{13}C NMR spectroscopy at different pH. Characteristic ^9Be NMR chemical shifts of **16–18** have been identified for the system. Gruenewald and Knoche [65] studied beryllium chelation with **11-14**. From chemical relaxation and stopped flow experiments, rates and equilibrium constants were reported for the formation of both BeL ($K = [BeL][H^+]/[Be(HL)^+] = (1 \pm 0.3) \times 10^{-3}$, $(2.2 \pm 0.2) \times 10^{-2}$, $(2 \pm 0.5) \times 10^{-3}$ and $(3 \pm 1) \times 10^{-4}$ dm^3 mol^{-1}, respectively) and $[Be(HL)]^+$ ($K = [Be(HL)^+]/[Be(OH)_2(HL)^+] = 17 \pm 2$, 18 ± 2, 30 ± 10 and 30 ± 10, respectively.

G. 2-AMINOCARBOXYLIC ACIDS (α-AMINO ACIDS)

2-Aminocarboxylic acids (or α-amino acids) and derivatives represent an important class of ligands that are biochemically relevant. On chelation, the dianionic moiety forms a five-membered ring with an N–O donor set (Fig. 13). In 1952 and 1953, Perkins [66,67] calculated equilibrium data for a whole range of α-amino acid derivatives (Table 4). The equilibrium data suggest that the overall formation constants, β_2, vary between 11 and 14. The substituents ranging from R = H to 2-amino(indol-3'-yl) groups appear to have insignificant consequences on the overall formation constant. Subtle changes were observed

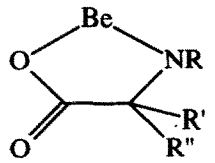
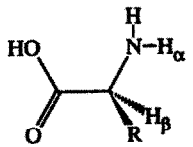


Fig. 13. Beryllium chelation of 2-aminocarboxylates.

TABLE 4



Formation constants of various bis-(2-aminocarboxylato)beryllium complexes

R	Amino acid	$\log_{10}\beta_2$
–H	Glycine (aminoacetic acid)	13.3
$-CH_3$	α-Alanine (2-aminopropanoic acid)	13.1
–H, $H_\alpha = CH_3$	Sarcosine (*N*-methylaminoacetic acid)	13.9
$-CH_2OH$	Serine (2-amino-3-hydroxypropanoic acid)	12.1
$-CH_2CO_2H$	Aspartic acid (aminobutandioic acid)	13.4
$-CH_2CONH_2$	Asparagine (2-aminobutandioic acid-4-amide)	11.7
–H, $H_\alpha = COCH_2NH_2$	Glycylglycine	9.8
$-CH_2CH_3$	2-Aminobutanoic acid	12.9
$-CH_3$, $H_\beta = CH_3$	2-Amino-2-methylpropanoic acid	12.4
$-CH(OH)CH_3$	Threonine (2-amino-3-hydroxybutanoic acid)	11.9
$-(CH_2)_2CO_2H$	Glutamic acid (2-aminopentandioic acid)	13.0
$-(CH_2)_2CONH_2$	Glutamine (2-aminopentandioic acid-5-amide)	12.4
$-(CH_2)_2CH_3$	Norvaline (2-aminopentanoic acid)	12.6
$-CH(CH_3)_2$	Valine (2-amino-3-methylbutanoic acid)	12.4
$-(CH_2)_3NH_2$	Ornithine (2,5-diaminopentanoic acid)	11.7
$-CH_2CH_2(SCH_3)$	Methionine [2-amino-4-(methylthio)-butanoic acid]	12.0
$-(CH_2)_3CH_3$	Norleucine (2-aminohexanoic acid)	12.8
$-CH(CH_3)CH_2CH_3$	DL-Isoleucine (2-amino-3-methylpentanoic acid)	12.6
$-CH_2CH(CH_3)_2$	DL-Leucine (2-amino-4-methylpentanoic acid)	13.2
$-(CH_2)_3NHCONH_2$	L-Citrulline (2-amino-5-ureidopentanoic acid)	13.0
$-(CH_2)_4NH_2$	Lysine (2,6-diaminohexanoic acid)	11.4
$-(CH_2)_3NHC(=NH)NH_2$	Arginine (2-amino-5-guanidopentanoic acid)	12.4
$-CH_2Ph$	3-Phenylalanine	11.9
$-CH_2$(Ph-*p*-OH)	Tyrosine [2-amino-3-(4'-hydroxyphenyl)propanoic acid]	11.1
–CH(OH)Ph	3-Phenylserine	11.1

due to different substituents but essentially the same N–O donor set preserves the same value of stability. The variation only reflect the differences of ionization constants observed between the different ligands. Therefore, so long as the α-amino acid moiety is not sterically impeded, then the likely overall stability constants can be roughly estimated on the basis of the ionization constants of the α-amino acid moiety. That is, a linear pK_a–$\log_{10}\beta_2$ relationship is observed.

H. 1,3-DIKETONES (β-DIKETONES)

The preparation of $Be(acac)_2$ **(19)** was first reported in the late 1800s by Combes [68]. Numerous crystalline 1,3-diketonate derivatives of beryllium have since appeared in

the literature. In general, 1,3-diketonato complexes of the alkaline earth metals are well described [69,70]. Bis-(1,3-diketonato) complexes with a tetrahedrally coordinated beryllium atom was demonstrated by experiments ranging from optical activity in asymmetric 1,3-diketonato derivatives to X-ray crystallographic studies. The existence of optical isomers was first demonstrated for complexes of beryllium in 1924 by Burgess and Lowery [71] who observed that solutions of beryllium benzoylcamphor undergo a rapid mutarotation. Two years later, Mills and Gotts [72] resolved bis-(benzoylpyruvato)-beryllium stereoisomers through the formation of its brucine salt. Resolution of the bis-(benzoylacetonato)beryllium complex has been achieved on active quartz, or by co-precipitation [73,74]. Variable temperature ^{1}H NMR spectroscopy on prochiral isopropyl derivatives (e.g. isobutyrylacetone and benzoylisobutyrylmethane) failed to separate the resonances characteristic for this optical activity [75]. Various attempts have been made to obtain the correct structure for **19** and recently Onuma and Shibata [76] determined the X-ray structure at 119 K for improved accuracy. Crystals of **19** were found to contain two independent molecules (Fig. 14). The geometry around the beryllium atom is distorted tetrahedral with O–Be–O angles in the range 106.9(2)–112.6(2)°. The structure is in good agreement with the results previously determined, by both X-ray diffraction at room temperature [77] and gas-phase electron diffraction studies [78].

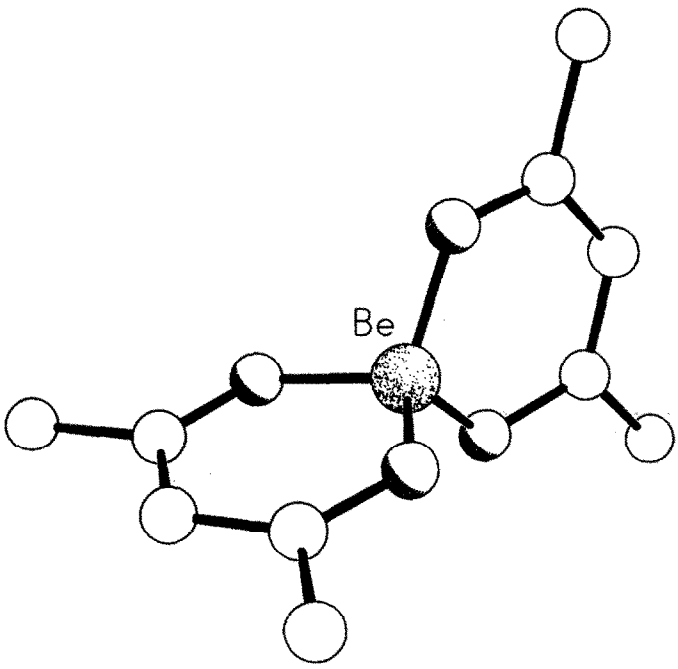
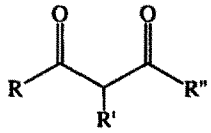


Fig. 14. X-Ray structure of bis-(acetylacetonato)beryllium.

TABLE 5



Formation constants of some 1,3-diketonato beryllium complexes

R	R'	R"	$\log_{10} K_1$	$\log_{10} K_2$	Ref.
CH_3	H	CH_3	12.36	10.94	79, 80
CH_3	CH_3	CH_3	11.36	10.15	80
CH_2OCH_3	H	CH_3	11.20	ppt.	80
CH_2OCH_3	CH_3	CH_3	11.65	10.23	80
CH_2OCH_3	C_2H_5	CH_3	11.89	10.65	80
CH_2OCH_3	n-C_3H_7	CH_3	11.88	10.76	80
CH_2OCH_3	n-C_4H_9	CH_3	11.83	10.64	80
Ph	H	Ph	13.62	12.41	79, 80
Ph	CH_3	Ph	12.36	ppt.	80
Mes	H	CH_3	11.02	10.05	81
Mes	H	Ph	11.79	11.12	81
Mes	H	Mes	10.66	9.74	81

Equilibrium studies have been reported for a number of 1,3-diketonato beryllium complexes (Table 5). In 1962, Martin and Martin [80] suggested that, in general, a linear pK_a–$\log_{10} K$ relationship is followed for 1,3-diketonato beryllium complexes (cf. α-amino acids). However, there were notable exceptions and these were attributed to various types of steric interactions which may have direct or indirect consequences on the chelating ability of the ligand. A few years later, Uhlemann and Frank [81] extended the study with equilibrium data for mesitoylacetone, mesitoylbenzoylmethane and dimesitoylmethane derivatives. Ribeiro da Silva and co-workers [82] studied standard enthalpies of formation of some 1,3-diketonates of beryllium. The mean beryllium–oxygen homolytic bond enthalpies were essentially the same for different 1,3-diketonates; however, the values differ (by ca. 10%) on changing to the aluminium analogue, possibly reflecting the difference in electrostatic forces of the two metal ions.

Kunz et al. [83] reported the major fragmentation pathways observed in the mass spectra of partially fluorinated bis-(1,3-diketonato)beryllium complexes. Apart from the molecular ion, initial fragmentation proceeds by the loss of the fluorine substituent. The loss of the $CF_3^{\cdot}$ radical is preferred to the loss of a $CH_3^{\cdot}$ radical due to the higher stability of the $CF_3^{\cdot}$ radical. In the same paper, Kunz et al. also describe ^{9}Be NMR studies of these complexes. The ^{9}Be NMR chemical shift for **19** is 2.97 ppm. Substitution of successive CF_3 groups results in an upfield shift; this is consistent with the increased electron-withdrawing ability of substituents. However, the trend is reversed on changing from

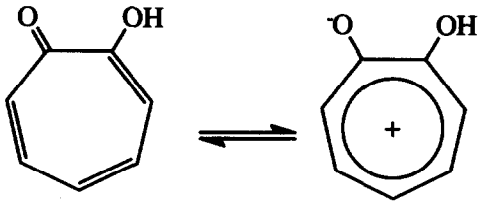


Fig. 15. Tautomerism of tropolone **20**.

CF_3 to C_2F_5 to C_3F_7 which suggests that electronegativity is not the only criterion in the correlation of ^9Be chemical shifts.

I. TROPOLONES

Tropolone (2-hydroxycyclohepta-2,4,6-trien-1-one) (**20**) is a seven-membered conjugated carbocyclic compound. Previous theoretical work suggests that **20** may represent a non-benzenoid aromatic system which possesses a resonance stabilization tautomer (Fig. 15). It is now generally accepted that the contribution from the dipolar resonance form is small but that **20** and derivatives can be conveniently rationalized as the enol forms of 1,2-diketones. On complexation, **20** derivatives form five-membered as opposed to six-membered chelate rings displayed by the analogous 1,3-diketones. In many respects they share the same ligation properties, except that in general, **20** derivatives form less stable beryllium complexes. Another significant reason for the interest in **20** derivatives is that they represent the key structural element in a wide range of natural products, many of which display interesting biological activity [84].

Derivatives of **20** are comparatively difficult to synthesize and despite the potential interest in these ligands as chelates for metal ions, the amount of work described is rela-

TABLE 6

Formation constants of some tropolonato beryllium complexes

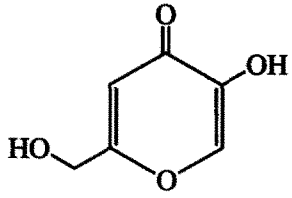
Ligand	log10 K_1[a]	$\log_{10} K_2$[a]
Tropolone	8.4, 7.4[b]	7.0
3-Methyltropolone	10.3	9.0
4-Methyltropolone	9.4	7.7
3-Isopropyltropolone	10.7	9.1
4-Isopropyltropolone	9.1, 7.0[c]	7.5
3,4-Benzotropolone	9.2	7.9
4,5-Benzotropolone	8.8	7.4
3-Bromotropolone	8.1	7.3

[a]Ref. 85, unless otherwise stated.
[b]Ref. 86.
[c]Ref. 87.

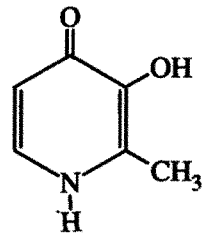
tively modest; this is especially true for metals such as beryllium. Equilibrium studies (Table 6) on various tropolonato beryllium complexes were first described by Bryant and Fernelius in 1953–1954 [85]. Since then, there have been few studies on tropolonato beryllium complexes. Hirai and Oka [86] have redetermined the stability constants of the **20** beryllium system and correlated $\log_{10} K_1$ with the ionization potentials of various bivalent metal ions. Inamo et al. [87] have made a detailed study of 4-isopropyltropolone (hinokitiol or β-thujaplicin) with beryllium by variable pressure and temperature, kinetic and equilibrium experiments in acidic aqueous solution. On the basis of these results, they discuss the reaction mechanism for the complexation of beryllium(II) ion. They propose that the intermediate, $[Be(H_2O)_3(LH)]^{2+}$ (unidentate ligation), undergoes rapid ring closure to form $[Be(H_2O)_3L]^+$ (bidentate ligation).

J. 3-HYDROXY-4-KETO-HETEROCYCLICS

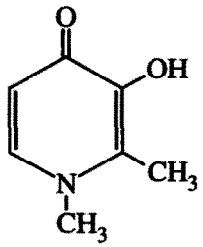
These are a group of ligands related to the tropolones and 1,3-diketones. The pyrone derivatives have been known for a long time (e.g. maltol has been reported to be a natural product of several plants [88]). The pyridinone derivatives have a more recent history, and is exemplified in nature by mimosine. These ligands represent recent develop-



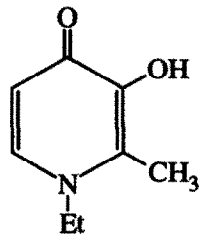
Kojic acid



3-Hydroxy-2-methylpyridin-4-one



1,2-Dimethyl-3-hydroxy-pyridin-4-one



1-Ethyl-3-hydroxy-2-methylpyridin-4-one

Scheme 2. 3-Hydroxy-4-keto-heteroaromatics.

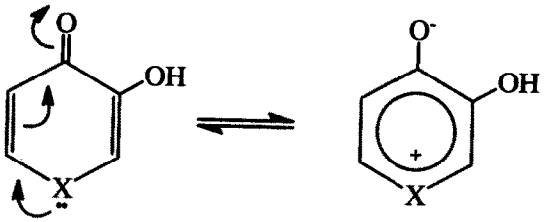


Fig. 16. Tautomerism of 3-hydroxy-4-keto-heterocycles.

ment in the chelation therapy of iron overload. Fe^{III} is another hard metal ion and the success of the pyridinones in clinical trials has further stimulated interest in them as chelators for toxic metals [89–91].

The ligands have a pseudo-aromatic tautomer formed by π donation from the heteroatom into the six-membered ring (Fig. 16). Equilibrium studies on the kojate beryllium complexes (Table 7) indicate that these ligands give formation constants comparable to the tropolones. We were unable to cite other quantitative data relating these type of ligands with beryllium, however Evans and Wong [93] have recently reported the formation constants of various pyridinones determined by ^9Be NMR spectroscopy. The quantitative study was carried out by integral analysis of the NMR data over a wide pH range. The ^9Be NMR spectra revealed separate resonances for the $[Be(H_2O)_4]^{2+}$, $[BeL]^+$ and $[BeL_2]$ species (Fig. 17). These were used to calculate the stepwise formation constants directly. The results indicate the stability constants are consistent with that found for the kojic acid derivative. The data suggest that the unusually strong chelation of pyridinones observed with Fe^{III} does not apply to the Be^{II} cation.

K. CATECHOL AND RELATED DIHYDROXYAROMATICS

Catechol (1,2-dihydroxybenzene) (**21**) and its derivatives are well known for both their ability to chelate strongly to metal ions and their "non-innocent" ligand behaviour. Many examples are found in nature and examples include gallic acid, pyrogallol, humic and tannic acids, dopamine, etc. The coordination of catechols has been widely studied for a range of transition metals [94], however the corresponding complexes for the main

TABLE 7

Formation constants of some 3-hydroxy-4-keto-heteroaromatic derivatives of beryllium

Ligand	log10 K_1	log10 K_2	Reference
Kojic acid	10.7	7.81	92
3-Hydroxy-2-methylpyridin-4-one	8.4	7.2	93
1,2-Dimethyl-3-hydroxypyridin-4-one	8.7	7.4	93
1-Ethyl-3-hydroxy-2-methylpyridin-4-one	8.5	7.3	93

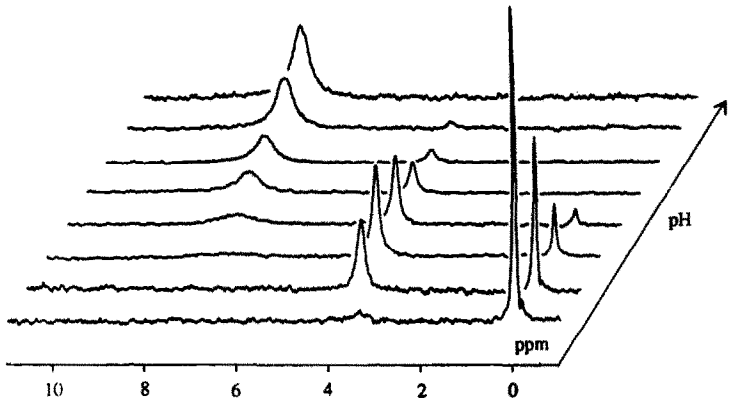
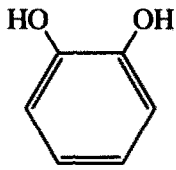
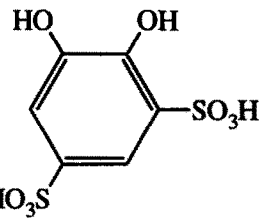


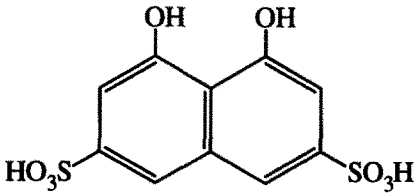
Fig. 17. Stack plot of ^{9}Be NMR spectra for the $Be(dmp)_x$ system over a pH range between 2 and 8, where dmpH = 1,2-dimethyl-3-hydroxypyridin-4-one and $x = 1$ or 2. The $[Be(H_2O)4]^{2+}$ ion is referenced at δ, 0; $[Be(dmp)]^{+}$ occurs at δ ca. 4; and $[Be(dmp)_2]$ occurs at δ ca. 7.5 ppm (38.0 MHz, H_2O with D_2O lock).



Catechol
(1,2-Dihydroxybenzene)



Tiron (4,5-Dihydroxy-1,3-benzenedisulphonic acid)



Chromotropic acid (4,5-Dihydroxy-naphthalene-2,7-disulphonic acid)

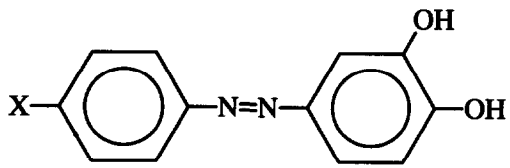
Scheme 3. Catechol and related dihydroxyaromatics.

TABLE 8

Formation constants of some dihydroxyaromatic derivatives of beryllium

Ligand	$\log_{10} K_1$	$\log_{10} K_2$	Reference
Catechol (1,2-dihydroxybenzene)	13.70	12.02	97
	13.52	9.83	98
Tiron (4,5-dihydroxybenzene-1,3-disulphonic acid)	13.5 ± 0.1	12.5 ± 0.1	99
	12.88	9.37	98
	12.20	9.30	93
DOPA (3,4-dihydroxyphenylalanine)		$\beta_2 = 11.6$	67
Lawsone (2-hydroxy-1,4-napthaquinone)	5.62	4.62	92
Chromotropic acid (4,5-dihydroxynaphthalene-2,7-disulphonic acid)	16.34	11.85	98
	16.20	12.00	93
1-Hydroxyanthraquinone	12.01	11.44	92
1,8-Dihydroxyanthraquinone		11.44	92
1,2-Dihydroxyanthraquinone-3-sulphonic acid	10.96		98

group elements have been less well studied. Rosenheim and Lehmann [95] first reported the synthesis of bis-(catecholato)beryllium by the reaction of beryllium hydroxide in alkaline solutions of **21**. Recent catecholato beryllium complexes have been reported mainly with regard to their therapeutic merit. Tiron (4,5-dihydroxy-1,3-benzene-disulphonic acid) (**22**) has received the most attention in this group of chelates. The sulphonate substituents provide both increased water solubility and reduced oxidation to semiquinones and benzoquinones. Basinger et al. [96] found that **22** was the most effective antidote for the treatment of beryllium intoxication in mice. As chelates, the equilibrium data (Table 8) suggest that a related ligand, chromotropic acid (4,5-dihydroxynaphthalene-2,7-disulphonic acid) (**23**) is by far the strongest chelate. Essentially both **22** and **23** provide similar phenolic O_2 donor sets; and the difference in ionization constants does not reflect the observed difference in stability. It may indicate the preference of the Be^{II} ion for six-membered chelate rings to five-membered chelate rings as demonstrated in the oxalate



X = H, CH_3, Cl, SO_3H, NO_2

Fig. 18. Monoazo derivatives of catechol [4-substituted-benzene-(1-azo-1'-)-3',4'-dihydroxybenzene].

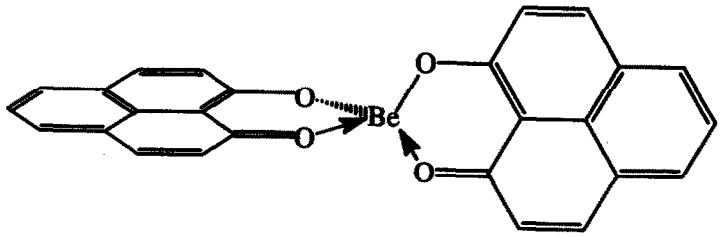
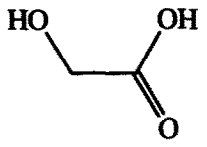


Fig. 19. Structure of bis-(9-oxidophenalenonato)beryllium.

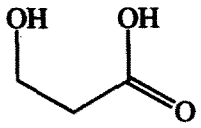
and malonate analogues described earlier. The quinones and hydroxyquinones have softer oxygen donors and as a consequence, lower stabilities, reflecting the "hard" nature of the Be^{II} cation.

Reaction of azo derivatives of catechol (Fig. 18) with beryllium have been studied by Basargin et al. [100]. The formation constants for the 1:1 ligand/metal complexes were determined spectrophotometrically ($-\log_{10} K_1$ = 8.4, 7.8, 7.5, 6.6 and 5.6 for X = CH_3, H, Cl, SO_3H and NO_2. respectively). A correlation was made between the formation constant and the variation of ionization constants of the ligand caused by the electronic effects of substituent X.

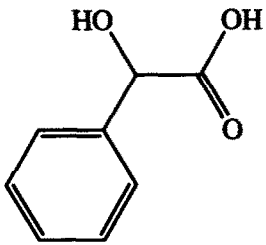
The X-ray crystal structure of bis-(9-oxidophenalenonato)beryllium has been determined [101]. This represents the only solid state structure determined for complexes



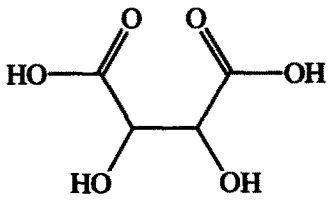
Glycollic acid
(Hydroxyacetic acid)



3-Hydroxypropanoic
acid



Mandelic acid
(2-Hydroxy-2-phenylacetic acid)



Tartaric acid
(2,3-Dihydroxybutanedioic acid)

Scheme 4. Aliphatic hydroxycarboxylic acids.

TABLE 9

Formation constants of some aliphatic hydroxy acid derivatives of beryllium

Ligand	$\log_{10} K_1$	Reference
Glycollic acid (hydroxyacetic acid)	1.49 ± 0.01	102
3-Hydroxypropanoic acid	1.53 ± 0.01	102
Mandelic acid (2-hydroxy-2-phenylacetic acid)	1.64 ± 0.01	102
Tartaric acid (2,3-dihydroxybutanedioic acid)	2.89 ± 0.03	103
	2.57 ± 0.01	104

derived from this set of ligands. The structure resembles that of the 1,3-diketone analogue with approximate tetrahedral geometry at the beryllium centre (Fig. 19). In the same paper, the electron delocalization of the complex was studied by electrochemistry and ESR spectroscopy.

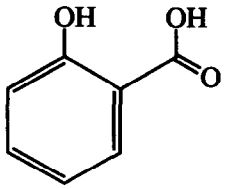
L. ALIPHATIC HYDROXYCARBOXYLIC ACIDS

Complexation of aliphatic hydroxy acids to beryllium is usually weak (Table 9) due to the nature of the ligand. Firstly, unlike the carboxylic acids, the hydroxy group is much less likely to deprotonate, thus making chelation more difficult. Secondly, the sp^3 carbon adjacent to the hydroxy group twists the potential chelate ring out of plane and increases the size of bite. Both features result in unfavourable chelation and in some cases the acids act as unidentate ligands using the ionized carboxylate oxygen only.

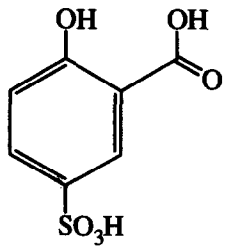
M. SALICYLIC ACIDS

The salicylic acid derivatives are the most widely studied group of ligands for the chelation therapy of beryllium poisoning. There are numerous examples of naturally occurring salicylates (e.g. humic acids) which are known to bind to metal ions [105,106]. Beryllium salicylate has been of biological interest since it was first described in 1924 [95], however the X-ray crystal structure of beryllium salicylate dihydrate has only recently been reported (Fig. 20) [107]. Previously, $BeL \cdot 2H_2O$ [108] was formulated as $BeL \cdot 3H_2O$ [109] and $Be(OH)(LH) \cdot 2H_2O$ [110].

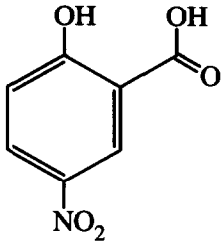
As a consequence of the low solubility of the salicylic acid itself, the sulphonated analogue, 5-sulphosalicylic acid **24** is often used for solution studies. Banks and co-workers [111] first reported equilibrium data for these beryllium complexes. Several independent workers have also determined equilibrium constants for various beryllium salicylate systems (Table 10). The salicylato moiety is formed by ionization of both the carboxylate and the phenolate protons. The aromaticity of the phenolate moiety makes for easier ionization and the resultant chelate ring is planar (cf. aliphatic hydroxycarboxylic acids). The substituent effects on the formation constants of beryllium salicylates have been described by Evans and Wong [93]. The electronic differences between 5-nitrosalicylic acid and 5-sulphosalicylic acid are small and this is reflected in the formation constants. The in-



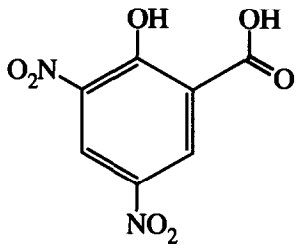
Salicylic acid



5-Sulphosalicylic acid



5-Nitrosalicylic acid



3,5-Dinitrosalicylic acid

Scheme 5. Salicylic acids.

creased electronegativity of 3,5-dinitrosalicylic acid over 5-nitrosalicylic acid decrease the ionization constant of the ligand. As a consequence, the formation constants of the 3,5-dinitrosalicylate beryllium system have also been lowered compared with the 5-nitrosalicylate beryllium system. This reflects the similarity between the proton and the Be^{2+} cation. That is, as with the 2-aminocarboxylates and 1,3-diketonates there is, in general, a linear pK_a–$\log_{10} K$ relationship for the complexes in solution.

TABLE 10

Formation constants of some salicylate beryllium complexes

Ligand	$\log_{10} K_1$	$\log_{10} K_2$	Reference
Salicylic acid	12.45	8.50	112
	12.61	9.99	61
	12.37	9.65	98
5-Sulphosalicylic acid	11.52	8.90	112
	11.54	8.89	98
	11.2	8.5	93
5-Nitrosalicylic acid	10.1	8.0	93
3,5-Dinitrosalicylic acid	7.8	5.5	93

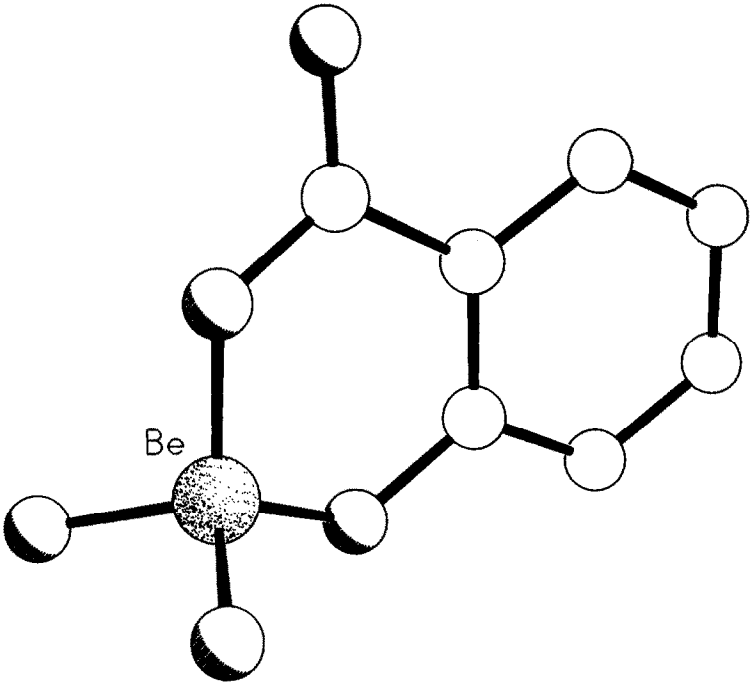


Fig. 20. X-Ray structure of beryllium salicylate dihydrate.

N. AURIN TRICARBOXYLIC ACID

Aurin tricarboxylic acid (ATA, Fig. 21) is used as an analytical reagent for the determination of Al^{III} in solution, hence the trivial name, aluminon, has often been adopted. Following the first quantitative studies of the Be–ATA system by Kosel and Neuman

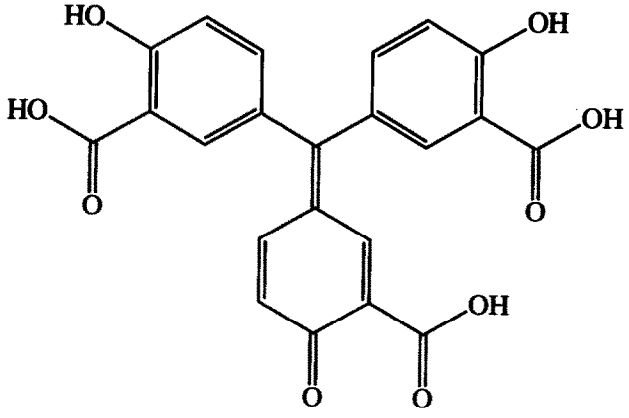
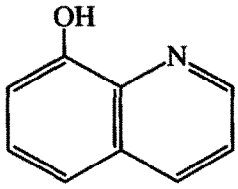
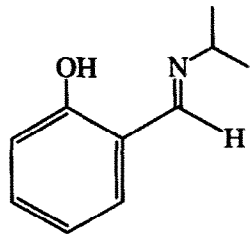


Fig. 21. Structure of aurin tricarboxylic acid, ATA.

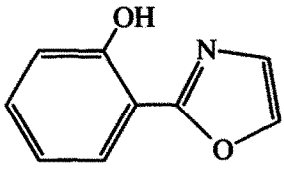
[113]; Lindenbaum, White, Schubert and co-workers [114–120] investigated the effectiveness of ATA as an antidote for acute experimental beryllium poisoning in mice. The chemical composition of ATA is essentially that of three salicylic acid derivatives joined together at the 5- position by a carbon atom. Each salicylate moiety is an effective chelate, and in solution one or more of the salicylate moieties chelate with beryllium which results in an insoluble compound or "lake formation". This effectively immobilizes the Be^{2+} ion and thus inactivates the toxicity. Unfortunately, unless ATA is administered in time, irreversible cellular damage will occur. Thrun [121] indicated that two molecules of ATA to one of Be are necessary for lake formation, but that an excess of about 20:1 is required to give maximum stability to the lake. In view of the number of biological experiments carried out using ATA, its coordination chemistry remains weak. The stability of the Be–ATA complex is more than ten times greater than that formed by salicylic acid and more than three times greater than that formed by **24** [118]. The greater effectiveness of ATA compared to the other compounds were principally ascribed to it forming a much stronger chelate and because it is bound far more strongly to proteins (where the ionized Be^{2+} are aggregated). Contrary to these early experiments, Basinger et al. [96] found that ATA was not as effective as some other simple chelates such as **22**.



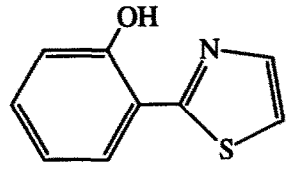
Oxine
(8-Hydroxyquinoline)



N-Isopropylsalicylaldimine



2-(*o*-Hydroxyphenyl)-
benzoxazole



2-(*o*-Hydroxyphenyl)-
benzothiazole

Scheme 6. Miscellaneous chelates.

O. MISCELLANEOUS CHELATES

The crystal structure of an N–O chelate, **4**, determined by Faure et al. [25] has already been discussed.

8-Hydroxyquinoline (oxine) and substituted derivatives have been investigated with various M^{3+} cations: tris-(8-hydroxyquinolinato) and tris-(8-hydroxy-2-methylquinolinato) (**25**) complexes have been successfully prepared for various M^{3+} cations with one notable exception, the Al^{3+} cation, which did not form the tris-chelate with **25**. This has been attributed to the very small size of the Al^{3+} ion causing substantial steric hindrance of the 2-methyl groups in a hypothetical complex. The even smaller Be^{2+} ion however forms the analogous bis-chelate (Fig. 22) [122]. The steric hindrance has been compensated for by the change from octahedral to tetrahedral geometry.

Bottino et al. [123] have used variable temperature ^1H NMR spectroscopy to investigate the free energy of activation (22.1 kcal mol^{-1} at 139°C) of the enantiomerization process in bis-(*N*-isopropylsalicylaldiminato)beryllium complex in 1,2-dichlorobenzene. The enantiomerization process was found to be reversible with no decomposition or bond rupture processes occurring. The free energy was comparable to the reported values in other optically active systems [71,72].

Few examples exist where beryllium is chelated solely to nitrogen donors. Beryllium-phthalocyanine (Fig. 23) has been successfully prepared by Linstead and coworkers [124]. The geometry of the molecule forces the beryllium to adopt a planar configuration in contrast to its normal tetrahedral arrangement. It is therefore not surprising that the complex is unstable and hydrolyses to form the dihydrate where presumably the

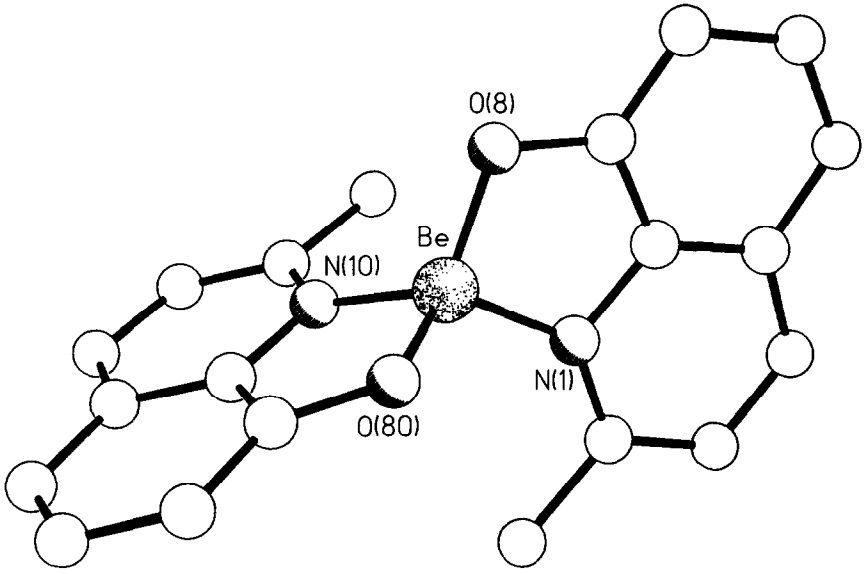


Fig. 22. X-Ray structure of bis-(8-hydroxy-2-methylquinolinato)beryllium.

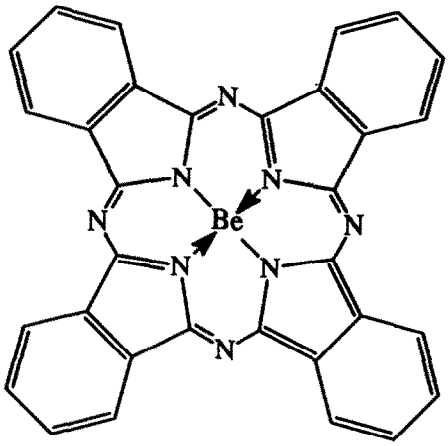


Fig. 23. Structure of the beryllium–phthalocyanine complex.

two Be–N bonds are broken and replaced by water molecules at distorted tetrahedral angles.

Gladilovich and Stolyarov [125] studied beryllium complexes derived from 2-(*o*-hydroxyphenyl)benzoxazole (**26**) and 2-(*o*-hydroxyphenyl)benzothiazole (**27**) by spectrophotometric and luminescence methods, and found that at least three complexes are formed: BeL^+, Be(OH)L and BeL_2. By a comparison of **26** and **27** beryllium derivatives, sulphur donors were considered too soft for chelation.

P. CONCLUSIONS

The beryllium cation binds strongly to hard oxygen donors. There are few examples of strong Be–N bonds and sulphur donors are non-existent. Unidentate ligands usually bind weakly and have a tendency to be replaced by hydroxyl moieties. Bidentate catecholate and salicylates have the most favourable properties. Both types of chelates possess hard oxygen donors with easily ionizable protons due to π electron delocalization. The catecholates form five-membered chelate rings whilst the salicylates form six-membered chelate rings. The geometry of the six-membered chelates gives a smaller bite which is favoured by the small Be^{2+} ion. The linear pK–$\log_{10}\beta_2$ relationship observed for a number of systems reflect the similarities of the Be^{2+} ion with the H^+ ion.

There are at present no Be^{II} specific sequestering agents. ATA, which possesses three salicylate moieties, remain the primary antidotal agent for beryllium poisoning. There is obvious potential for designing specific encapsulating ligands which have ideal tetrahedral cavity for the Be^{II} ion.

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